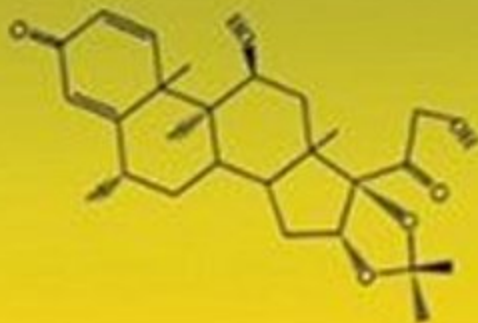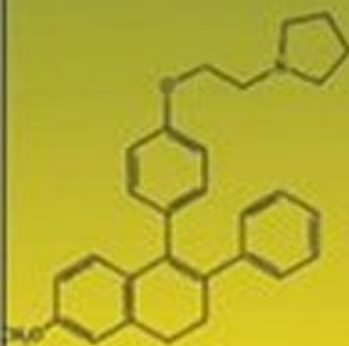Daniel Lednicer

Strategies for Organic Drug Synthesis and Design

STRATEGIES FOR ORGANIC DRUG SYNTHESIS AND DESIGN

STRATEGIES FOR ORGANIC DRUG SYNTHESIS AND DESIGN

Second Edition

DANIEL LEDNICER

WILEY

A JOHN WILEY & SONS, INC., PUBLICATION

To the memory of now-defunct laboratories where once I practiced my craft: Building H at G.D. Searle in Skokie, Upjohn's Building 25 in Kalamazoo and the diminutive Chemistry Annex at the Adria Laboratories just outside Dublin, Ohio.

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PREFACE

"One of the most interesting aspects of organic chemistry is that of dealing with the building-up of complex substances from simpler ones. The synthesis of organic compounds, whether for scientific or industrial purposes, has been very important in the development of the science and is still of great importance today."

Those words, set down 80 years ago as the opening for a chapter on organic synthesis in Conant's pioneering textbook *Organic Chemistry*,* still very aptly describes the important role held by that aspect of the discipline. The use of organic transformations for the preparation of compounds with more or less complex structures has had a profound influence on both organic chemistry and, more importantly, on modern civilization. One need only bring to mind medicinal agents at one extreme and, on the other, the monomers used for the plethora of polymers that have provided the basis for a whole new materials science. The practice of organic synthesis covers an extremely broad range, from the highly practical, economically driven preparation of a tonnage chemical to a multistep, very elegant enantiospecific synthesis of a complex natural product. This very diversity may account for the relative paucity of books devoted specifically to the subject.

The manipulation used for the preparation of therapeutic agents seems to offer a middle ground between those extremes in complexity. The published syntheses for these agents are typically relatively short, seldom exceeding 10 or so steps. The target compounds for these syntheses do, however, cover a very wide range of structural types, encompassing both carbocyclic and heterocyclic compounds. The chemistry moreover includes a very broad selection of organic reactions. The published syntheses most often describe the route that was used in the discovery of

*Conant, James B.; *Organic Chemistry*, Macmillan, New York, 1928, p. 117.

some new compound. Some exotic and versatile reagents are used since reaction conditions are not circumscribed by their applicability to plant processes. The syntheses of therapeutic agents thus offer a good didactic tool.

The first edition of this book comprised a selection of syntheses from the five-volume series *The Organic Chemistry of Drug Synthesis* that was in press at that time. Examples were chosen to illustrate the strategy and the organic transformations that were used to prepare the various structural classes that had been investigated as drugs. Research over the decade that has elapsed since the appearance of that first edition saw the birth of many new drugs and perhaps, more importantly, drugs that addressed new therapeutic areas. These also on occasion invoked the use of novel chemistry. These new developments strongly suggested that it was time to bring the book up to date. Many of these new developments are included in this second edition of *Strategies for Organic Drug Synthesis and Design*. This new work is taken from the two volumes of *The Organic Chemistry of Drug Synthesis* that appeared after the publication of the first edition (Volume 6, 1999, Volume 7, 2008).

One of the main motivations that led to the writing of the original book, entitled *The Organic Chemistry of Drug Synthesis*, was curiosity as to how various classes of drugs were in fact prepared. The enormous number of compounds reported in the literature as potential drugs led to an early decision to restrict the book to those agents that had been granted nonproprietary names. This filtering mechanism was based on the assumption that, in the judgment of the sponsor, the compound in question showed sufficient activity to merit eventual clinical evaluation. Within a few years of the publication of *The Organic Chemistry of Drug Synthesis*, a followup volume was issued to bring the coverage up to date and to make up for gaps in the coverage of the original book. Between them, the two books included a large majority of compounds that had been granted generic names up to that time. The subsequent three volumes of what became a series appeared roughly semidecenial in order to cover the syntheses of compounds granted generic names during those intervals. A full decade elapsed before the most recent volume appeared due to a slowdown in the appearance of new compounds granted USAN.

The focus of this book differs from that of the series in that it is aimed more specifically at the organic chemistry used for preparation of the drugs in question. Drugs have been selected mainly for the illustrative value of the chemistry used for their synthesis, and hence, too, the inclusion of the rather extensive "Reaction Index." The structures in chemical schemes have been drawn with special attention to clarifying the individual reactions; rearrangements, starting materials, and products, for example, are shown in similar views. The very brief discussions of medicinal chemistry are intended to provide the reader with a feel for the activities and occasionally the mechanisms of action of various drugs. Salient principles of drug action are presented in capsule form at appropriate points; by the same token, the claimed therapeutic effect of each agent is noted along with the discussion of its preparation. The pharmacological presentations are thus abbreviated over those that occur in the series. Interested readers should consult any of a wide selection of medicinal chemistry or pharmacology texts such as *Burger's Medicinal Chemistry* for fuller and more authoritative discussions.

A word on bibliographic references is in order at this point. The patents that comprise a significant proportion of references were often not readily accessible 10 years ago; to help the reader, those were usually accompanied by a reference to that patent recorded in *Chemical Abstracts*. The ready availability of actual images to U.S. patents (www.uspto.gov) and those from abroad (http://ep.espacenet.com) has led to the deletion of the now-superfluous *Chemical Abstracts* reference.

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DANIEL LEDNICER
North Bethesda, MD
March 2008

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CHAPTER 1

PROSTAGLANDINS, PEPTIDOMIMETIC COMPOUNDS, AND RETINOIDS

1.1. PROSTAGLANDINS

It is highly likely that those not themselves involved in scientific research perceive the development of new knowledge within a given area of science as a linear process. The popular view is that the understanding of the specific details of any complex system depends on prior knowledge of the system as a whole. This knowledge is in turn believed to derive from the systematic stepwise study of the particular system in question. The piecemeal, almost haphazard, way in which the details of the existence and later the detailed exposition of the arachidonic acid cascade were put together is much more akin to the assembly of a very complex jigsaw puzzle. This particular puzzle includes the added complication of incorporating many pieces that did not in fact fit the picture that was finally revealed; the pieces that would in the end fit were also found at very different times.

The puzzle had its inception with the independent observation in the early 1930s by Kurzok and Lieb [1] and later von Euler [2] that seminal fluid contained a substance that caused the contraction of isolated guinea pig muscle strips. The latter named this putative compound prostaglandin in the belief that it originated in the prostate gland; the ubiquity of those substances was only uncovered several

decades later. The discovery remained an isolated oddity until the mid-1960s, by which time methods for chromatographic separation of complex mixtures of polar compounds and spectroscopic methods for structure determination were sufficiently advanced for the characterization of humoral substances that occur at very low levels. The isolation and structural assignment of the first two natural prostaglandins, PGE_1 and PGF_2, were accomplished by Bergstrom and his colleagues at the Karolinska Institute [3]. (The letter that follows PG probably initially referred to the order in which the compounds were isolated: E refers to 9-keto-11-hydroxy compounds and F refers to 9,11-diols; the subscripts refer to the number of double bonds.) The carbon atoms of the hypothetical, fully saturated, but otherwise unsubstituted carbon skeleton, prostanoic acid, are numbered sequentially starting with the carboxylic acid as 1, and then running around the ring and resuming along the other side chain.
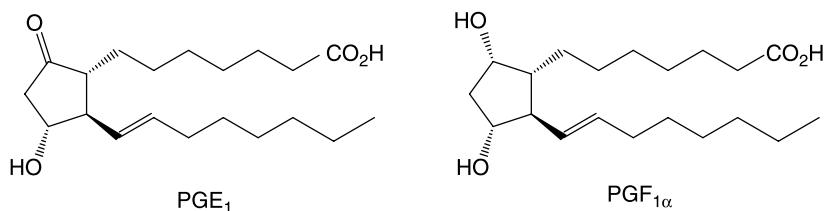
The identification of these two prostaglandins in combination with their very high potency in isolated muscle preparations suggested that they might be the first of a large class of new hormonal agents. Extensive research in the laboratories of the pharmaceutical industry had successfully developed a large group of new steroid-based drugs from earlier similar leads in that class of hormones; this encouraged the belief that the prostaglandins provided an avenue that would lead to a broad new class of drugs. As in the case of the steroids, exploration of the pharmacology of the prostaglandins was initially constrained by the scarcity of supplies. The low levels at which the compounds were present, as well as their limited stability, forced the pace toward developing synthetic methods for those compounds. The anticipated need for analogues served as an additional incentive for elaborating routes for their synthesis.

Further work on the isolation of related compounds from mammalian sources, which spanned several decades, led to the identification of a large group of structurally related substances. Investigations on their biosynthesis made it evident that all eventually arise from the oxidation of the endogenous substance, arachidonic acid. The individual products induce a variety of very potent biological responses, with inflammation predominating. Arachidonic acid, once freed from lipids by the enzyme phospholipase A_2, can enter one of two branches of the arachidonic acid

cascade [4] (Scheme 1.1). The first pathway to be identified starts with the addition of two molecules of oxygen by a reaction catalyzed by the enzyme cyclooxygenase to give PGG$_2$. That enzyme, now known to occur in two and possibly three forms, is currently identified by the acronym COX; it is sometimes called prostaglandin synthetase. The reaction comprises the addition of one oxygen across the 9,11 positions to give a cyclic peroxide while the other adds to the 14 position in a reaction reminiscent of that of singlet oxygen to give a hydroperoxide at 14, with the resulting shift of the olefin to the 12 position and with concomitant isomerization to the *trans* configuration. The initial hydroperoxide is readily reduced to an alcohol to give the key intermediate PGH$_2$. The reductive ring opening of the bridging oxide leads to the PGF series while an internal rearrangement leads to the very potent inflammatory thromboxanes. It was found later that aspirin and indeed virtually all nonsteroid anti-inflammatory drugs (NSAIDs) owe their efficacy to the inhibition of the cylcooxy-genase enzymes.

Scheme 1.1. Arachidonic Acid Cascade.
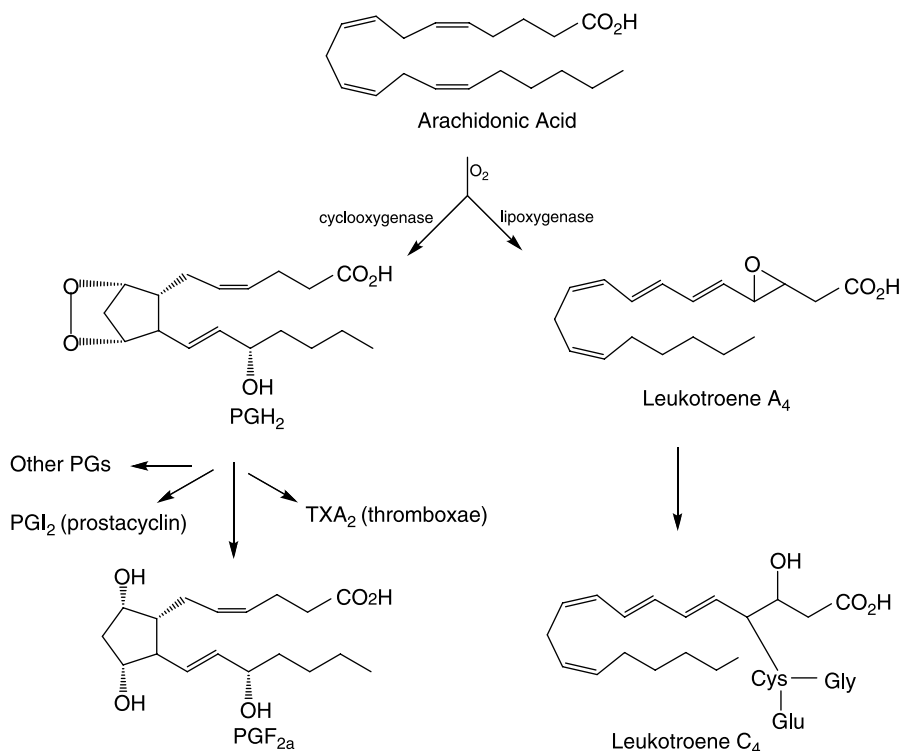
The reaction of arachidonic acid with the enzyme lypoxygenase (LOX), on the other hand, leads to an attack at the 5 position and rearrangement of the double bonds to the 7,9-*trans*-11-*cis* array typical of leukotrienes; the initial product closes to an epoxide, thus yielding leukotriene A_4. The reactive oxirane in that compound in turn reacts with endogenous glutathione to give leukotriene C_4. This compound and some of its metabolites, it turned out, constitute the previously well-known "slow reacting substance of anaphylaxis" (srs-A), involved in allergic reactions and asthma.

Much of the early work on this class of compounds focused on developing routes for producing the agents in quantities sufficient for biological investigations. There was some attention paid to elaborating flexible routes as it was expected that there might be some demand for analogues not found in nature. This work was hindered by the relative dearth of methods for elaborating highly substituted five-membered rings that also allowed control of stereochemistry. The unexpected finding of a compound with the prostanoic acid skeleton in a soft coral, the sea whip *plexura homomalla* [5], offered an interim source of product. The group at Upjohn, in fact, developed a scheme for converting that compound to the prostagland, which they were investigating in detail [6]. The subsequent development of practical total syntheses in combination with ecological considerations led to the eventual replacement of that marine starting material.

The methodology developed by E. J. Corey and his associates at Harvard provides the most widely used starting material for prostaglandin syntheses. This key intermediate, dubbed the "Corey lactone," depends on rigid bicyclic precursors for controlling stereochemistry at each of the four functionalized positions of the cyclopentane ring. Alkylation of the anion from cyclopentadiene with chloromethylmethyl ether under conditions designed to avoid isomerization to the thermodynamically more stable isomer gives the diene (**3-1**). In one approach, this is then allowed to react with α-chloroacrylonitrile to give the Diels–Alder adduct (**3-2**) as a mixture of isomers. Treatment with an aqueous base affords the bicyclic ketone (**3-3**), possibly by way of the cyanohydrin derived from the displacement of halogen by hydroxide. Bayer–Villiger oxidation of the carbonyl group with peracid gives the lactone (**3-4**); the net outcome of this reaction establishes the *cis* relationship of the hydroxyl that will occupy the 11 position in the product and the side chain that will be at 9 in the final product. Simple saponification then gives hydroxyacid (**3-5**). The presence of the carboxyl group provides the means by which this can be resolved by conventional salt formation with chiral bases. Reaction of the last intermediate with base in the presence of iodine results in the formation of iodolactone; the reaction may be rationalized by positing the formation of a cyclic iodonium salt on the open face of the molecule; attack by the carboxylate anion will give the lactone with the observed stereochemistry. Acetylation of the hydroxyl gives (**3-6**); halogen is then removed by reduction with tributyltin hydride (**3-7**). The methyl ether on the substituent at the future 11 position is then removed by treatment with boron tribromide. Oxidation of the primary hydroxyl by means of the chromium trioxide : pyridine complex (Collins reagent) gives Corey lactone (**3-9**) as its acetate [7].
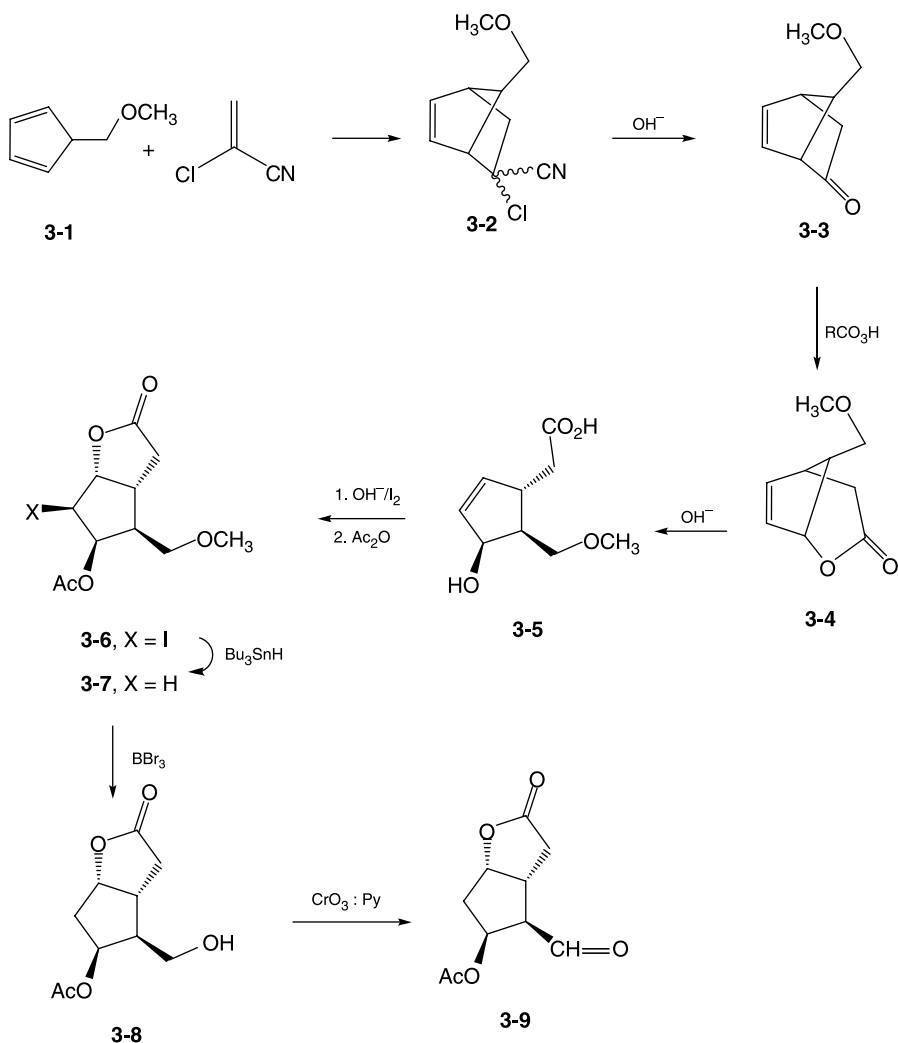
A somewhat more direct route to the Corey lactone, developed later, depends on a radical photoaddition/rearrangement reaction as the key step. The scheme starts with the Diels–Alder addition of α-acetoxyacrylonitrile to furan to give the bridged furan (**4-1**) as a mixture of isomers. Hydrolysis by means of aqueous hydroxide gives the ketone (**4-2**); this reaction may also proceed through the intermediate cyanohydrin. This cyanohydrin is in fact produced directly by treatment of the mixture of isomers with sodium methoxide in a scheme for producing the ketone in chiral form. The crude intermediate is treated with brucine. Acid hydrolysis of the solid "complex" that separates affords quite pure dextrorotary ketone (**4-2**) [8]; this complex may consist of a ternary imminium salt formed by a sequential reaction

with the cyanohydrin function. Irradiation of the ketone in the presence of phenylse-lenylmalonate leads to the rearranged product (**4-5**) in quite good yield. The structure can be rationalized by postulating the homolytic cleavage of the C-Se bond in the malonate to give intermediate (**4-3**) as the first step; the resulting malonate radical would then add to the olefin. Acyl migration would then give the rearranged carbon skeleton of (**4-4**). Addition of the phenylselenyl radical to that intermediate will then give the observed product. Reduction of the carbonyl group by means of sodium borohydride gives the product of approach of hydride from the more open *exo* face (**4-6**). Decarboxylation serves to remove the superfluous carboxyl group to afford (**4-7**); treatment with *tertiary*-butyldimethylsilyl chloride in the presence of imidazole gives the protected intermediate (**4-8**) that contains all the elements of the Corey lactone with the future aldehyde, however, in the wrong α configuration. Saponification of the ester followed by acid hydrolysis, in fact, gives the all *cis* version of the lactone [9]. The desired *trans* isomer (**4-9**) can be obtained by oxidizing the selenide with hydrogen peroxide in the presence of sodium carbonate [10].
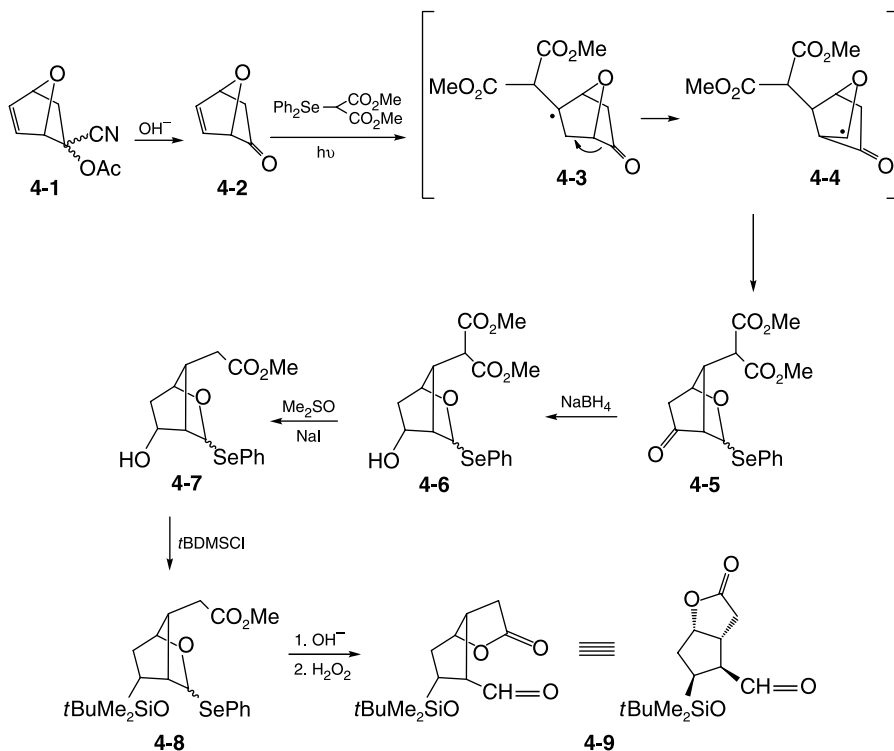
Biological investigations, once supplies of prostaglandins were available, revealed the manifold activities of this class of agents. The very potent effect of

PGF$_{2\alpha}$ on reproductive function was particularly notable. Ovulation in most mammalian species is marked by the formation on the ovary of a corpus luteum that produces high levels of progesterone if a fertile ovum has implanted in the uterus. Administration of even low doses of PGF$_{2\alpha}$ was found to have a luteolytic effect, with loss of the implanted ovum due to the withdrawal of progestin. This prostaglandin was in fact one of the first compounds in this class to reach the clinic under the United States Adopted Name (USAN) name **dinoprost**. The development of drugs for use in domestic animals tends to be faster and much less expensive than those that are to be used in humans. This is particularly true if the animals are not used as food, since this dispenses with the need to study tissue residues. It is of interest, consequently, that one of the early prostaglandins that reached the market is **fluprostenol** (**5-8**). This compound differs from PGF$_{2\alpha}$ in that the terminal carbon atoms in the lower side chain are replaced by the trifluromethylphenoxy group; this modification markedly enhances potency as well as stability. This drug is marketed under the name Equimate® for controlling fertility in racing mares, a species in which costs are probably of little consequence.

Reaction of the anion from phosphonate (**5-1**) with ethyl *meta*-trifluorophenoxymethylacetate results in acylation of the phosphonate by the displacement of ethoxide and the formation of (**5-3**). Condensation of the ylide from this intermediate with the biphenyl ester at position 11 of Corey lactone (**5-4**) leads to the enone (**5-5**) with the usual formation of a *trans* olefin expected for this reaction. The very
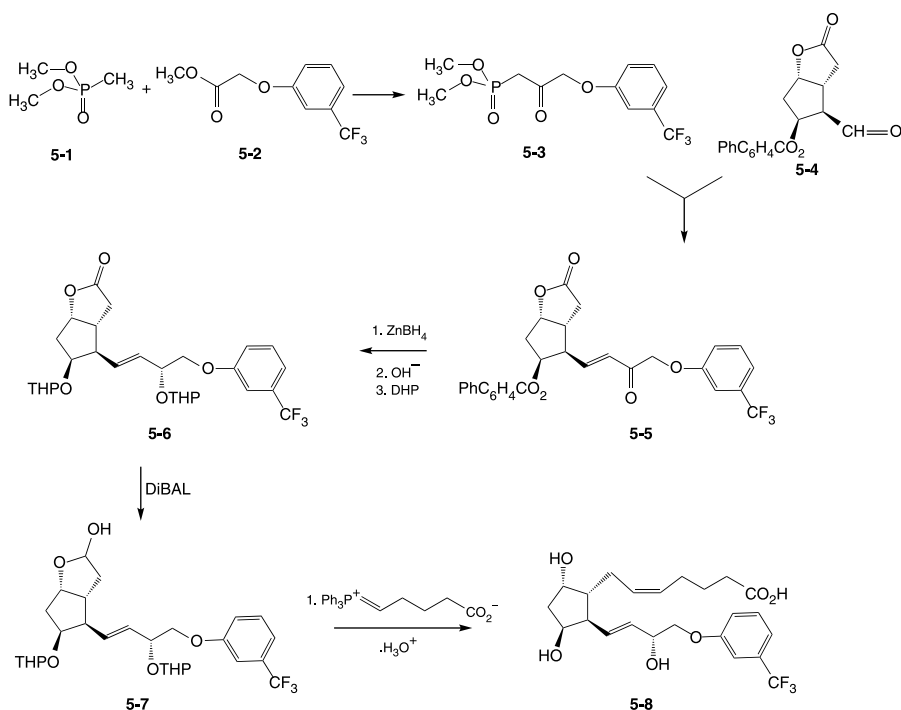
bulky biphenyl ester comes into play in the next step. Reduction of the side chain ketone by means of zinc borohydride proceeds to give largely the 15α alcohol as a result of the presence of that bulky group. The ester is then removed by saponification, and the two hydroxyl groups are protected as their tetrahydropyranyl ethers (**5-6**). The next step in the sequence involves the conversion of the lactone to a lactol; the carbon chain is thus prepared for attachment of the remaining side chain while revealing potential hydroxyl at the 9 position. This transform is affected by treating (**5-6**) with diisobutylaluminum hydride at −78°C; over-reduction to a diol occurs at higher temperatures. Wittig reactions can be made to yield *cis* olefins when carried out under carefully defined, "salt-free" conditions [11]. Condensation of the lactol (**5-7**) with the ylide from 5-triphenyl-phosphoniumpentanoic acid under those conditions gives the desired olefin. Treatment with mild aqueous acid serves to remove the protecting groups, thus forming **fluprostenol** (**5-8**) [12].

Prostaglandins have been called hormones of injury since their release is often associated with tissue insult. Most of these agents consequently exhibit activities characteristic of tissue damage. Many prostaglandins cause vasoconstriction and a consequent increase in blood pressure as well as the platelet aggregation that precedes blood clot formation. Thromboxane A_2 is, in fact, one of the most potent known platelet aggregating substances. Prostacyclin, PGI_2, one of the last cyclooxygenase products to be discovered, constitutes an exception; the compound causes vasodilation and inhibits platelet aggregation. This agent may be viewed formally as the cyclic enol ether of a prostaglandin that bears a carbonyl group at the 6 position of the upper side chain. This very labile functionality contributes to the short half-life of PGI_2. The fact that the lifetime of this compound is measured in single-digit minutes precludes the use of this agent as a vasodilator or as an inhibitor of platelet aggregation.

PGI_2

Prostacyclin
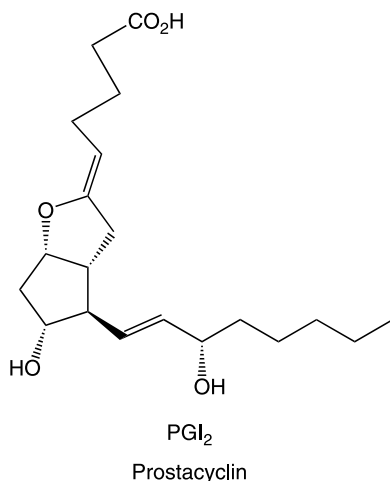
The analogue in which carbon replaces oxygen in the enol ring should of course avoid the stability problem. The synthesis of this compound initially follows a scheme similar to that pioneered by the Corey group. Thus, acylation of the ester (**7-2**) with the anion from trimethyl phosphonate yields the activated phosphonate (**7-3**). Reaction of the ylide from that intermediate with the lactone (**7-4**) leads to a compound (**7-5**) that incorporates the lower side chain of natural prostaglandins. This is then taken on to lactone (**7-6**) by sequential reduction by means of zinc borohydride, removal of the biphenyl ester by saponification, and protection of the hydroxyl groups as tetrahydropyranyl ethers.
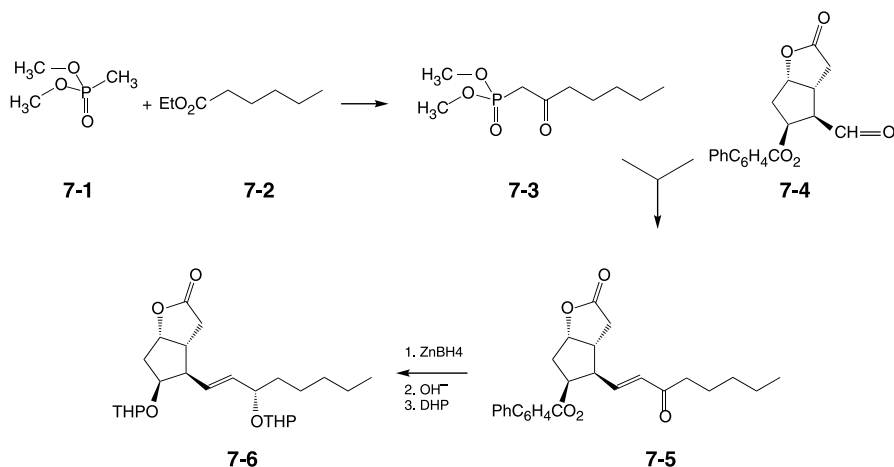
The first step in building the carbocyclic ring consists, in effect, of a second acylation on trimethyl phosphonate. Thus, the addition of the anion from that reagent to the lactone carbonyl in (**7-6**) leads to the product as its cyclic hemiketal (**8-1**); this last, it should be noted, now incorporates an activated phosphonate group. Oxidation of that compound with Jones' reagent gives the diketone (**8-2**). The ylide prepared from that compound by means of potassium carbonate in aprotic media adds internally to the ring carbonyl group to give fused cylopentenone (**8-3**). Conjugate addition of a methyl group to the enone by means of the cuprate reagent from methyl lithium occurs predominantly on the open β face of the molecule to afford (**8-4**). The counterpart of the upper side chain is then added to the molecule by condensation with the ylide from triphenylphosphoniumpentanoic acid bromide. The product (**8-5**) is obtained as a mixture of E and Z isomers about the new olefin due to the absence of directing groups. Removal of the tetrahydropyran protecting groups with mild aqueous acid completes the synthesis of **ciprostene** (**8-6**) [13]. This compound has the same platelet aggregation inhibitory activity as PGI$_2$, though with greatly reduced potency.
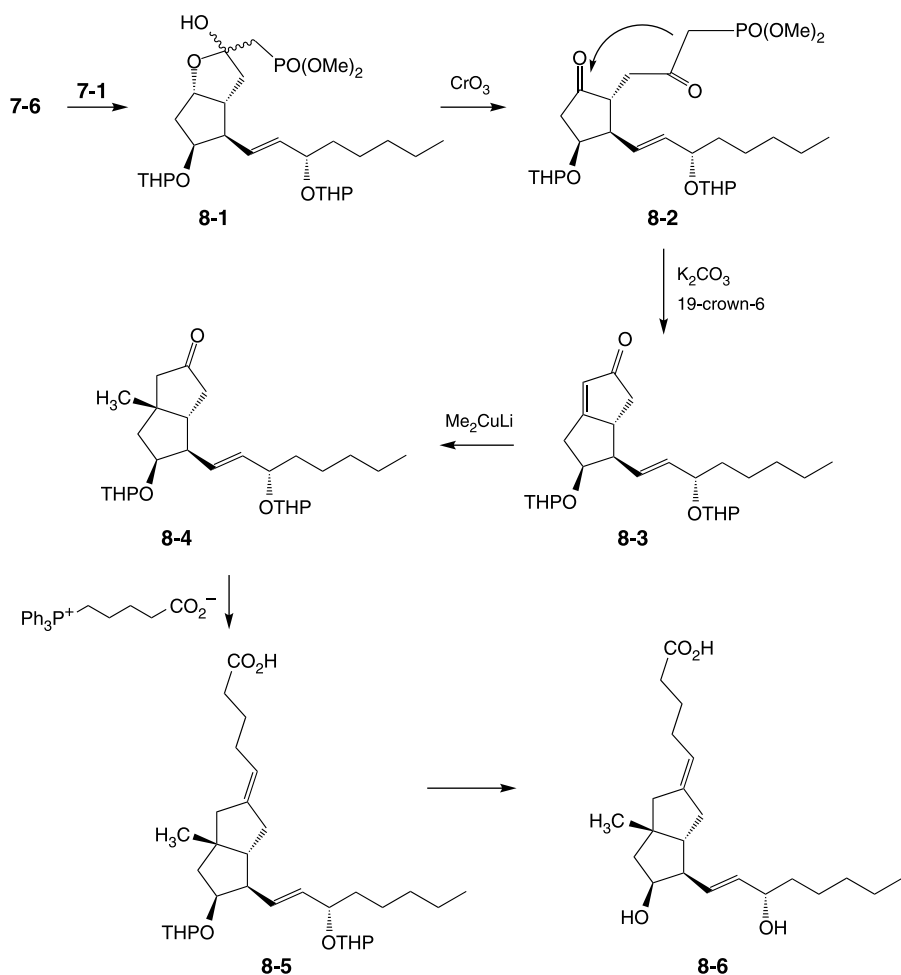
An analogue in which a fused tetralin moiety replaces the furan and part of the side chain in prostacyclin is approved for use as a vasodilator for patients with pulmonary hypertension. The lengthy, complex synthesis starts with the protection of the hydroxyl group in benzyl alcohol (**9-1**) by reaction with *tert*-butyl dimethyl siliyl chloride (**9-2**). Alkylation of the anion from (**9-2**) (butyl lithium) with allyl bromide affords (**9-3**). The protecting group is then removed and the benzylic hydroxyl oxidized with oxalyl chloride in the presence of triethyl amine to give the benzaldehyde (**9-4**). The carbonyl group is then condensed with the organomagnesium derivative from treatment of chiral acetylene (**9-5**) with ethyl Grignard to afford (**9-6**) (the triple bond is not depicted in true linear form to simplify the scheme). The next few steps adjust the stereochemistry of the newly formed

alcohol in (**9-6**). This group is first oxidized back to a ketone with pyridinium chlorochromate. Reduction with diborane in the presence of chiral 2-(hydroxy-diphenylmethyl)pyrolidine affords the alcohol as a single enantiomer. This is then again protected as its *t*BDMS ether (**9-7**). Heating this compound with cobalt carbonyl leads to the formation of the tricyclic ring system. Mechanistic consider-ations aside, the overall sequence to the product (**9-8**) involves eletrocylic formation of the six-membered ring from the olefin and the acetylenic bond as well as insertion of the elements of carbon monoxide to form the five-membered ring. Catalytic hydro-genation of that product (**9-8**) leads to a reduction of the double bond in the enone as well as hydrogenolyis of the benzylic *t*BDMS ether on the six-membered ring (**9-9**). Reduction of the ketone then leads to the alcohol, apparently as a single enantiomer. Acid hydrolysis leads to the loss of the tetrahydropyrany protecting group to afford intermediate (**9-10**). The presence of labile groups in this compound precludes the usual methods such as hydrogen bromide or boron tribromide for cleaving the
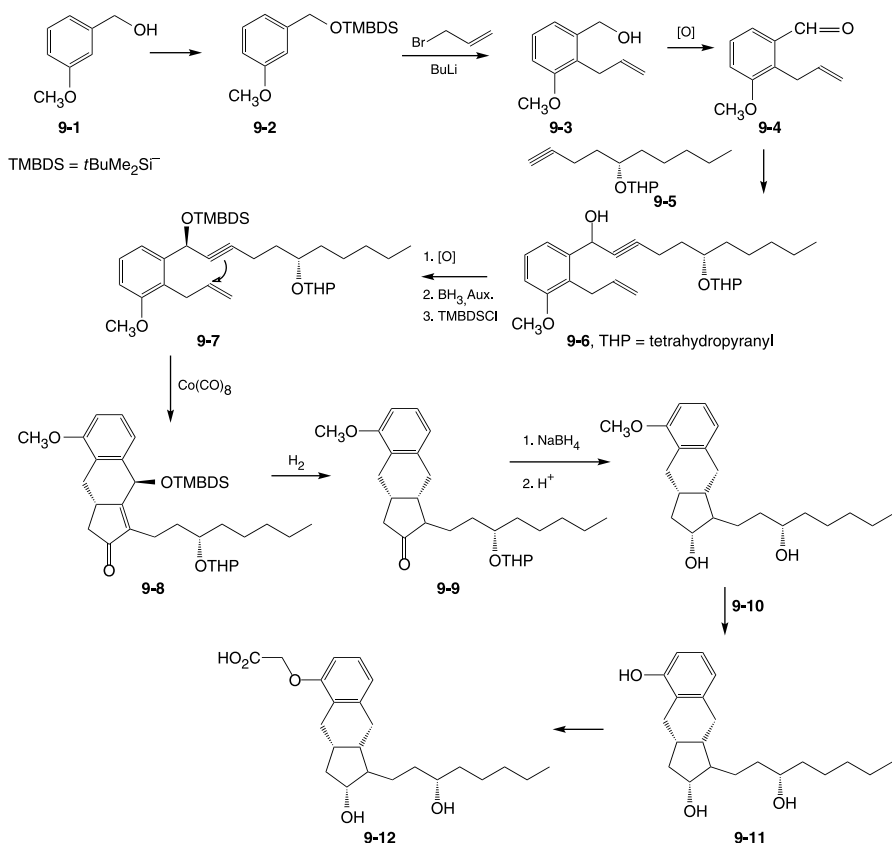
methyl ether. Instead, in an unusual sequence, phenol (**9-11**) is obtained by treatment of (**9-10**) with butyl lithium and diphenyl phosphine. The product is then alkylated with 2-chloroacetonitrile. Hydrolysis of the cyano group to an acid finally affords the vasodilator **treprostinil** (**9-12**) [14–16].

Dinoprost (PGF$_{2\alpha}$) was the first prostaglandin to be approved for clinical use. The specific indication comprised induction of labor. It has received some publicity recently as a result of its use as an adjunct in RU-486 (**mifepristone**; *see* Chapter 4) induced abortions. Though initial supplies of PGF$_{2\alpha}$ were obtained by partial synthesis from soft coral–derived starting materials, this was supplanted by a total-synthesis product. The reported synthesis, like those noted above, relies on a rigid fused bicyclic starting material for determining the relative configuration of the substituents on the cyclopentane ring.

The sequence starts by epoxidation of bicycloheptadiene (**10-1**) with peracid, a reaction that had been found earlier to proceed to aldehyde (**10-3**) rather than stopping at the epoxide. This rearrangement, which will control stereochemistry at positions 11, 12, and 15 in one fell swoop, is related conceptually to the *i*-steroid rearrangement discovered at least a decade earlier. The reaction relies in effect on the mobile equilibrium between a cyclopropylcarbinyl carbocation and its homoallyl partner: This rearrangement can be visualized as starting with the protonation of the initially formed epoxide to (**10-2**). This could then first ring open to an alcohol. The observed product (**10-3**) would be obtained by Wagner–Meerwin rearrangement of the resulting carbocation. The same product would be formed by the concerted reaction shown in the scheme below. The aldehyde is then protected as its acetal (**10-4**) with 2,2-dimethylpropylene glycol. The two carbon atoms that will form the upper side chain are then incorporated by electrocyclic addition of dichloroketene; the chlorine atoms are removed by reduction with zinc to give (**10-5**). Delaying the all-important resolution until a late step in the synthesis of chiral compounds invokes the penalty
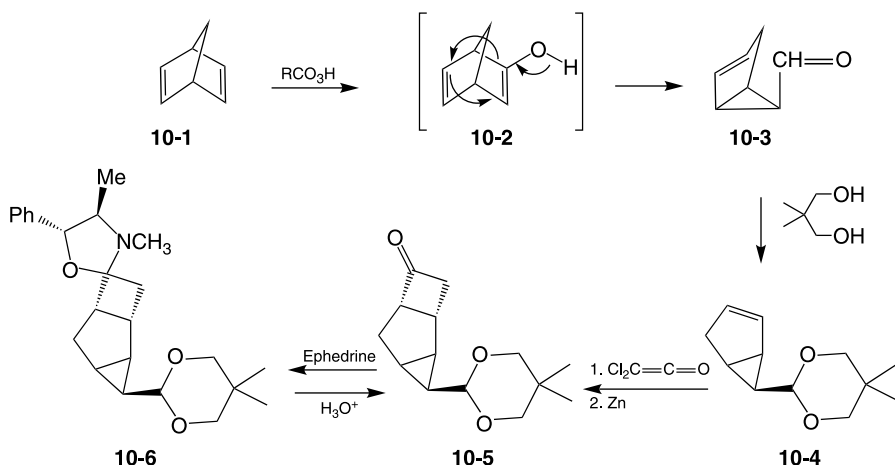
of carrying the useless inactive enantiomer through a large number of transformations. Efficient syntheses either incorporate the separation early or, better yet, start with chiral compounds. An unusual method is used to affect the resolution in the case at hand. Thus, condensation of fused cyclobutanone (**10-5**) with l-ephedrine affords a pair of diastereomeric oxazolidines (**10-6**); the higher melting of the pair providentially corresponds to the desired isomer. Separation followed by hydrolysis over silica gives (**10-5**) with the prostaglandin stereochemistry.

The cyclobutanone is then lactonized by means of Bayer–Villiger oxidation; treatment with dilute acid then serves to remove the acetal group to afford lactone-aldehyde (**11-2**). The next step comprises incorporating the remaining carbon atoms required for the lower side chain, Thus, Wittig condensation of the aldehyde with the ylide from triphenylphosphoniumhexyl bromide under salt-free conditions affords the *cis* olefin (**11-3**), which is converted to epoxide (**11-4**) by means of peracid. Solvolysis of this last intermediate in formic acid gives compound (**11-5**) accompanied by significant amounts of glycols; the mixture is recycled to give (**11-5**) in modest yield.
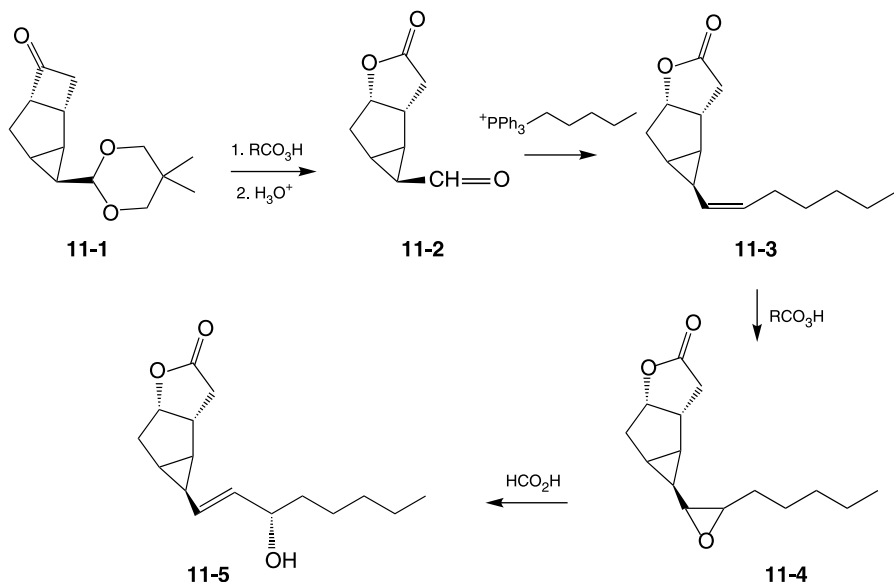
This rearrangement, which is in effect the reverse of that used to form the cyclopropyl ring in (**10-2**), can be visualized as starting with protonated epoxide (**12-1**); this can then go on to rearrange via a homoallyl ion (**12-2**); the observed stereoselective formation of the 11-hydroxyl argues for a concerted reaction. Solvolysis of the diol byproduct (**12-3**) may also go through carbocation (**12-2**) or through a more concerted transition state. The product (**12-4**) is finally taken on to $PGF_{2\alpha}$ by a sequence very similar to that used to first add the lower side chain to (**7-6**), and after suitable protection of the hydroxyls elaboration of the upper side chain [17,18].
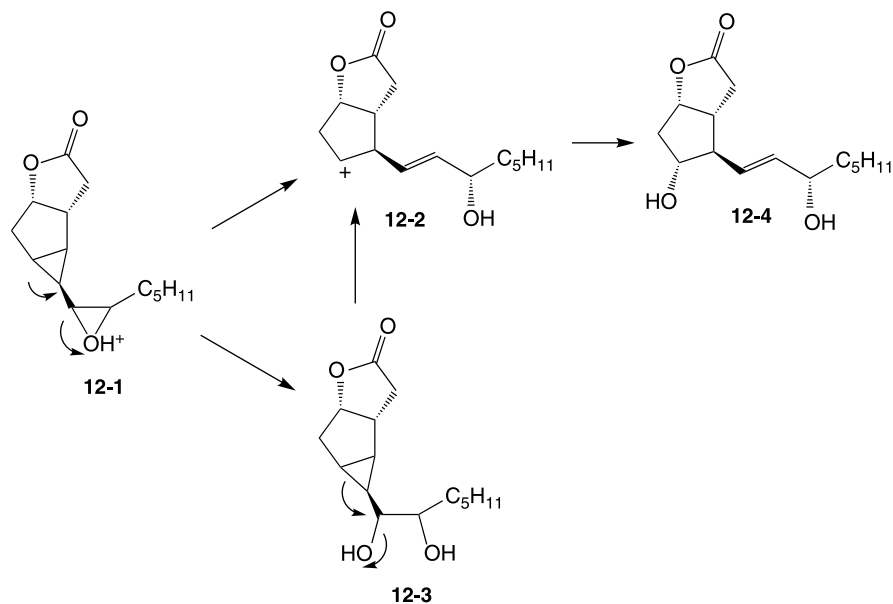
It has been known for some time that a mucus layer secreted by gastric cells protects the lining of the stomach from noxious agents, including its own digestive agents. Studies on the pharmacology of the prostaglandins revealed that these compounds had a cytoprotective effect on the gastric mucosa by maintaining the mucus layer. The recognition that aspirin and the pharmacologically related NSAIDs owed their action to the inhibition of cyclooxygenase, at the time thought to consist of a single enzyme, offered an explanation for their well-recognized injurious effect on gastric mucosa. Inhibition of that enzyme leads to a decrease in prostaglandin synthesis and a consequent increased vulnerability to irritants, including normal stomach acid. This prostaglandin deficit is difficult to remedy due to the manifold activity of most congeners, their very short biological half-life, and poor oral bioavailabilty. The finding that biological activity is retained when the side chain hydroxyl is moved from the prime site of metabolism, 15, to the 16 position eventually resulted in the development of misoprostol (**14-5**), a drug approved for the prevention of NSAID-induced ulcers.

The synthesis of this compound represents a notable departure from those discussed above. The presence of the carbonyl group at the 9 position of the cyclopentane ring, which classifies this compound as a PGE, removes one asymmetric center and thus somewhat reduces the stereochemical complexity of the synthesis. More importantly, this introduces the possibility of attaching the lower side chain by means of a 1,4-addition reaction; the *trans* relationship of the two side chains should be favored by thermodynamic considerations. The very unusual functionality of the required Michael acceptor, that of a cyclopent-2-en-4-ol-1-one, leads to a rather lengthy albeit straightforward synthesis for the requisite intermediate.

The scheme starts by activation of monomethylazeleiate (**13-1**) as its imidazole amide by means of thionyl bisimidazole. Condensation of that product with the *bis* anion from reaction lithium salt of monomethyl malonate gives acetoacetate (**13-2**); the first-formed tricarbonyl compound decarboxylates on workup. The two terminal methyl ester groups are then saponified to the corresponding acids; that β to the carbonyl group decarboxylates to a methyl ketone on acidification to afford (**13-3**). Acylation of this last intermediate with dimethyl oxalate leads to the addition of an oxalyl group to each carbon flanking the ketone to give an intermediate such as (**13-4**). (Both this and (**13-5**) are depicted as their unlikely all-ketone tautomers in the interest of clarity.) That intermediate cyclizes to the triketocyclopentane (**13-5**) under reaction conditions. Treatment with acid leads to a scission of the superfluous pendant oxalyl group. The product (**13-6**) probably exists as a mixture of the two possible enolates. Hydrogenation in the presence of palladium on charcoal interestingly leads to a reduction of the single carbonyl group not involved in that tautomerism to give the future prostaglandin 11 hydroxyl. Reaction of the product with acetone dimethyl acetal in the presence of acid leads initially to the formation of enol ethers; these can be forced to (**13-7**) because of its lower solubility in ether. Reduction of that (**13-7**) with lithium aluminum hydride or Vitride at $-60°C$ leads on workup to the enone (**13-8**).
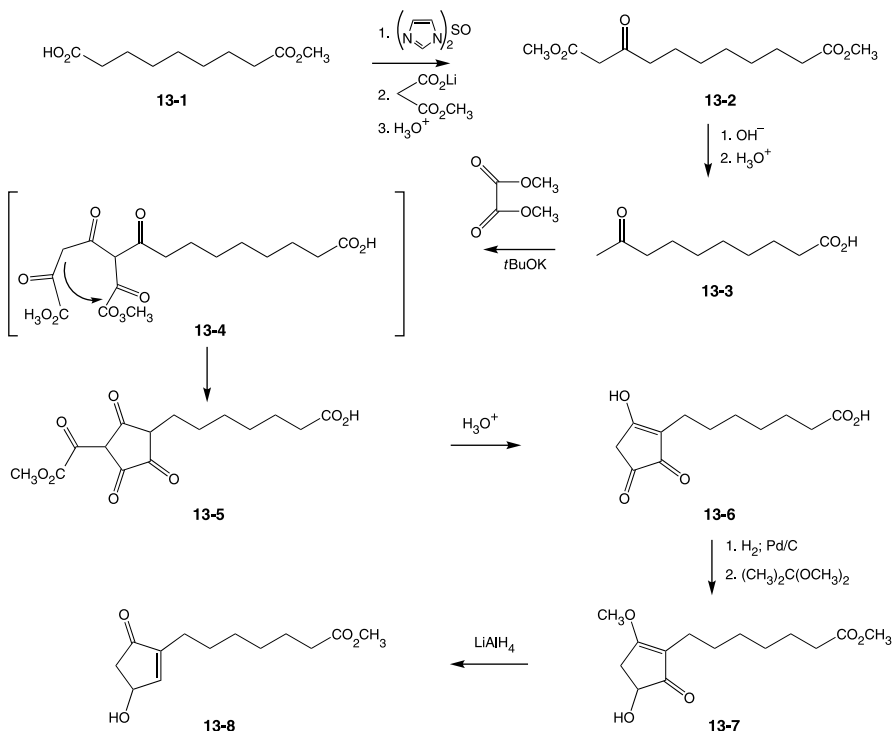
Preparation of the reagent required for adding the lower side chain involves a series of metal interchanges carried out as a one-pot reaction. The sequence starts by stereospecific stannylation of acetylene (**14-1**) by means of tributlytin hydride. Reaction of that with butyl lithium gives the corresponding vinyl lithio reagent, where the tin is replaced with retention of configuration. The lithium is then replaced by organocopper moiety by reaction with copper pentyne to give the cuprate reagent (**14-3**). The addition of (**14-3**) to the cyclopentenone as its silyl ether (**14-4**) gives the Michael product. Removal of the silyl protecting group affords **misoprostol (14-5)** as a mixture of enantiomers [19,20].
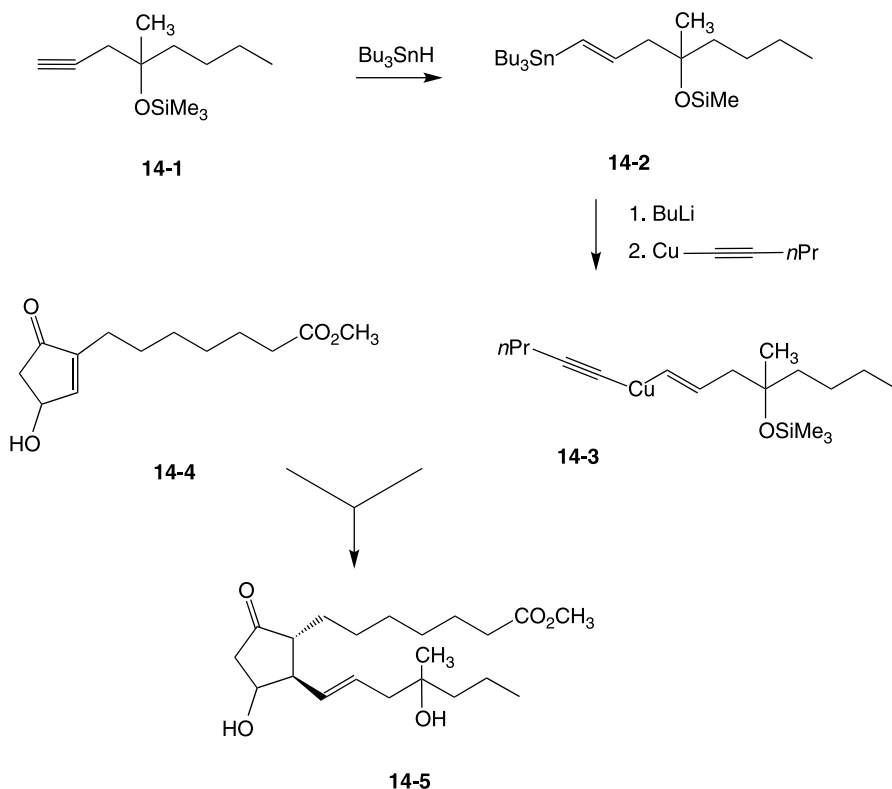
Among their many other activities, prostaglandins have a direct effect on the gastrointestinal (GI) tract. PGE_2, for example, regulates many physiological functions of the gut including mucosal protection, gastrointestinal secretion, and motility. A PGE-related compound, **lubiprostone (15-11)**, for example, increases both intestinal fluid secretion and motility. This compound has been recently approved for the treatment of chronic constipation and is being investigated as a treatment of constipation-predominant irritable bowel syndrome. It has been ascertained that the drug interacts with specific ion channels in the GI tract, causing increased fluid output into the lumen. The starting material for the synthesis (**15-1**) comprises a variant

on the Corey lactone. Condensation of this aldehyde with the ylide from the difluorinated phosphonate (**15-2**) leads to the addition product (**15-3**). The double bond in the olefin has the expected *trans* geometry, though the next step, hydrogenation, makes this point moot. Sodium borohydride then reduces the side chain ketone function to give (**15-5**) as a mixture of isomers. The lactone is next reduced to the key lactol in the usual fashion, by means of diisobutyl aluminum hydride (**15-6**). The product is then condensed with the ylide obtained from the reaction of the zwitterion 4-triphenylphosphoniumbutyrate to give the chain extended olefin (**15-7**). The carboxylic acid in this intermediate is next protected as the benzyl ester by alkylation of its salt with benzyl chloride (**15-8**). Oxidation of the ring alcohol by means of chromium trioxide followed by exposure to mild acid to remove the tetrahydropyranyl group establishes the keto-alcohol PGE-like function in the five-membered ring (**15-9**). Catalytic hydrogenation of this last intermediate at the same time reduces the remaining double bond and removes the benzyl protecting group on the acid to give the open chain version (**15-10**) of the product. The electron-withdrawing power of the fluorine atoms adjacent to the side chain ketone causes the carbonyl carbon to become a reasonable electrophile. The electron-rich oxygen on the ring alcohol thus adds to this to give a cyclic hemiacetal. This form (**15-11**) greatly predominates in the product **lubiprostone** [21].
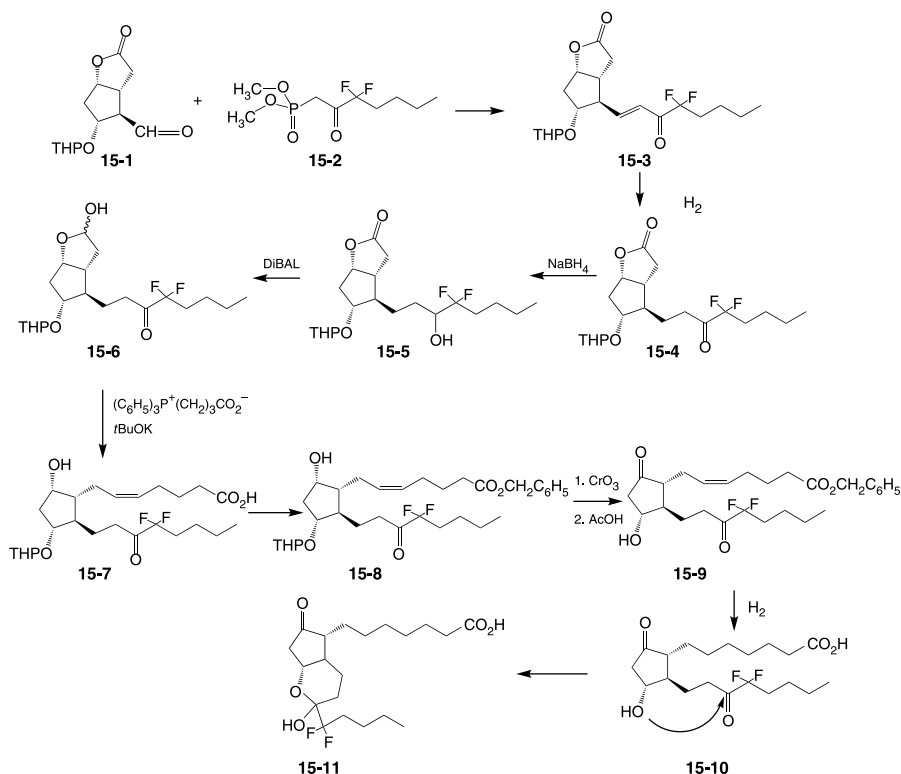
As noted previously, NSAIDs inhibit the inflammatory and, to some extent, the platelet-aggregating activities of products from the arachidonic cascade by inhibiting the enzyme, cylooxygenase, that catalyzes their formation. One of the few nitrogen-containing prostaglandin analogues, **vapiprost** (**16-9**), is reported to be an inhibitor of thromboxane A_2-induced platelet aggregation. This congener is potentially a more specific inhibitor of platelet aggregation, the prelude to thrombus formation, than NSAIDs in that it blocks thromboxane A_2 at the receptor site. Treatment of the chiral adduct (**16-1**) from ketene and cyclopentadiene with bromodimethylhydantoin in acetic acid results in the formation of bromoacetate (**16-2**), which results from the formal addition of hydrobromous acid. The stereochemistry of the product probably results from the formation of the initial bromonium ion on the more open face of the molecule. Treatment with piperidine leads to a rearrangement to a 2,2,1-bibcycloheptane with the incorporation of nitrogen on the new one-carbon bridge. The structure of the product can be rationalized by postulating an intermediate, or transition, species such as (**16-3**) along the reaction pathway. Saponification of the initially formed product gives keto-alcohol (**16-4**). This is acylated to (**16-5**) by means of *para*-biphenylacetyl halide, a bulky group used in other prostaglandin syntheses for directing the stereochemistry of reductions. Bayer–Villiger oxidation with peracid gives a bridged version (**16-6**) of a Corey lactone; reduction with diisobutylaluminum hydride in the cold leads to hydroxyaldehyde (**16-7**), here
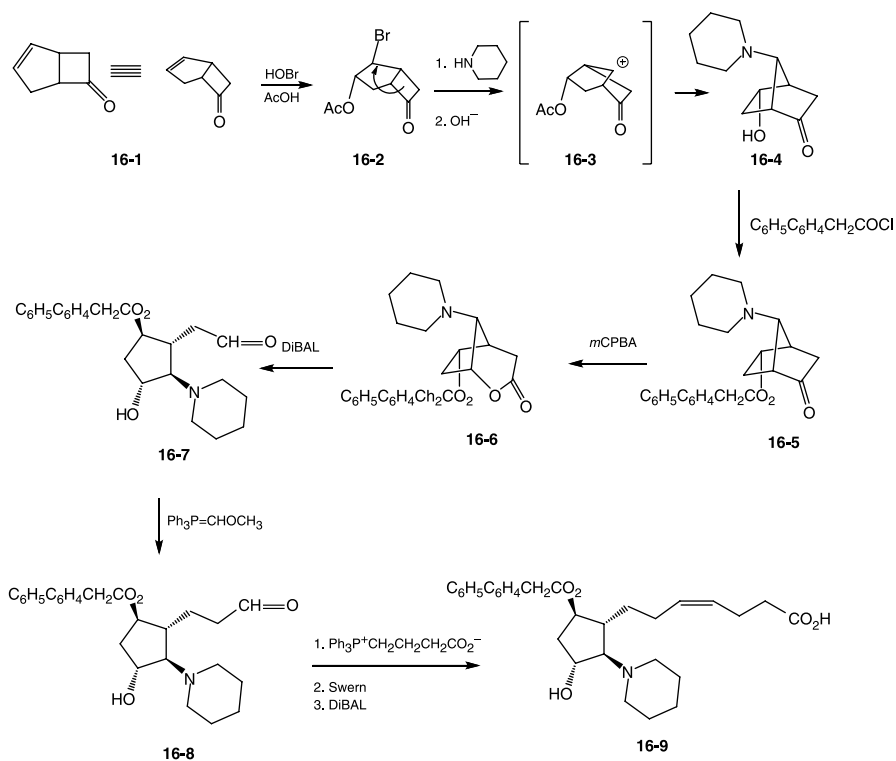
isolated in open form. The aldehyde is then first homologated by reaction with methoxymethyl phosphorane to give (**16-8**). A second Wittig condensation, with the ylide from triphenylphosphonium butyrate, completes the construction of the side chain that differs from that in natural prostaglandins in that the olefin is moved one atom closer to the terminal acid. The next two steps consist of inverting the stereochemistry of the 11 hydroxyl group to the unnatural β configuration. Thus, Swern oxidation of the initial product followed by reduction with diisobutylaluminum hydride gives **vapiprost** (**16-9**) [22]. The stereochemistry of the reduction is probably guided by the very bulky *para*-phenylbenzoyl group at the 9 position.

1.2. PEPTIDOMIMETIC COMPOUNDS

1.2.1. Protease Inhibitors

1.2.1.1. Introduction. The central role of polypeptides as regulators of life processes is of course very generally recognized. An important class of those regulators consists of enzymes, virtually all of which are made up of chains of amino acids. It is an interesting fact that these compounds, whose assembly is mediated by transcription of RNA, are quite frequently not synthesized directly in their final form. Instead, they quite often first appear as part of a much larger peptide; a specialized class of enzymes, dubbed proteases, cut the chain at specific locations so as to excise the enzyme in its active form. Renin was one of the first of the proteases to be investigated in some detail. This polypeptide specifically cleaves the large peptide angiotensinogen to excise therefrom the decapeptide angiotensin I. This last yields the potent vasoconstrictor octapeptide angiotensin II in reaction with yet another protease, an angiotensin-converting enzyme (ACE). A series of nonpeptide compounds that blunted the action of that enzyme, known as the ACE inhibitors, have proven useful in treating hypertension by decreasing levels of vasoconstricting angiotensin II by lowering levels of ACE. Considerable effort has been devoted to the search for drugs that block this cascade upstream at the level of renin in the search for antihypertensive agents that would avoid some of the shortcomings of the generally well-tolerated ACE inhibitors. This search has been rewarded with the development of several compounds that inhibit the cascade at its very inception by blocking the action of renin.

Proteases, like many enzymes, act by stabilizing a relatively high energy transition state; in this case the initial adduct of a hydroxyl group, or its functional equivalent, to the carbonyl carbon. This addition causes the geometry of that center to change from trigonal to tetrahedral. Known inhibitors consist of molecules that mimic an essential stretch of the protease recognition site and, most importantly, provide a sequence that duplicates the transition center sterically without, however, including a cleaveable bond. The fermentation product, pepstatin, a peptide-like inhibitor of pepsin, provided an early clue for the synthesis of protease inhibitors; the central portion of that molecule provides a 1,3-hydroxyamide sequence that is thought to act as a transition state analogue from a peptide bond; note that a methylene replaces one

amide nitrogen. The active moiety, statine, has been prepared by a total synthesis involving aldol-like condensation of isoleucylaldehyde with the lithio carbanion from acetate [23].

Transition State

Pepstatin Fragment   Statine

1.2.1.2. Renin Inhibitors. Preparation of the renin inhibitor **terlakiren** (**18-6**) starts with the reaction of the S-methyl ether of cysteine protected as its *tertiary*-butoxycarbonyl amide (BOC) (**18-1**) with the statine analogue (**18-2**), in which cyclohexyl replaces the isobutyl group; the coupling reaction is catalyzed by di-cyclohexylcarbodiimide (DCC). The amino group in product (**18-3**) is then

18-1   **18-2**

*t*BOC = Me₃COCO

18-3. R = *t*BOC
18-4. R = H

18-5

18-6

deprotected by treatment with trifluoroacetic acid; this reagent leads to the elimination of isobutylene from the BOC group followed by decarboxylation of the now-unstable free carbamic acid to afford free amine (**18-4**). The coupling sequence is now repeated using a phenyl alanine derivative (**18-5**) to yield the desired product (**18-6**) [24].

The enantioselective synthesis of a somewhat more complex renin inhibitor starts with the reduction of the ester group in the chiral amino-ester (**19-1**) by means of diisobutyl aluminum hydride in the cold. The aldehyde product (**19-2**) is then reacted with prior isolation with the ylide from phosphonium salt (**19-3**) and a strong base
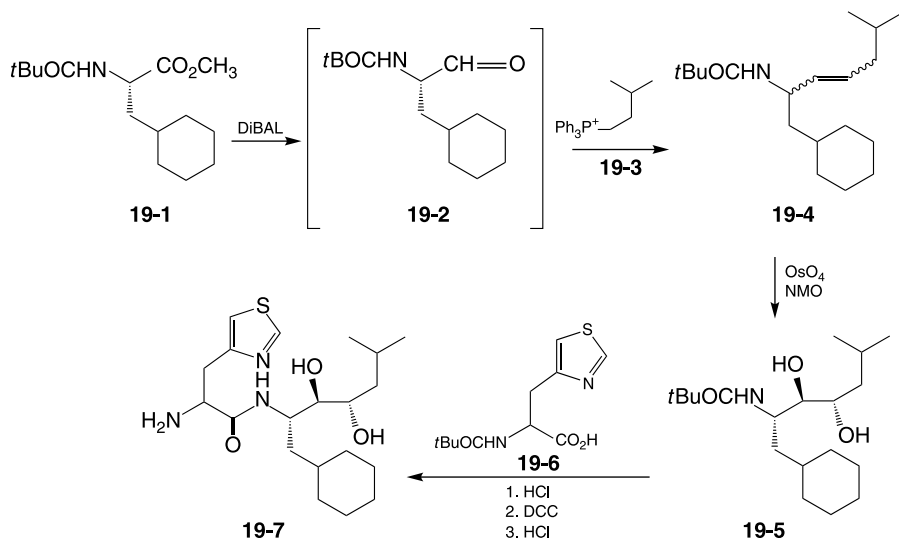
to give the olefin (**19-4**) as a mixture of geometric isomers. Oxidation of the product with *N*-methylmorpholine oxide (NMO) in the presence of a catalytic amount of osmium tetroxide leads to the *trans* glycol (**19-5**). Treatment with hydrogen chloride then cleaves the protecting group to afford the free amine. That intermediate is then coupled in the presence of DCC with the chiral thiazoloalanine (**19-6**). A second round of hydrogen chloride leads to the dipeptide-like intermediate (**19-7**).

The reaction of benzaldehyde with methyl acrylate in the presence of the non-nucleophilic base DABCO results in an unusual aldol condensation in which the product (**20-3**) results from the addition of the anion from the unsaturated olefin carbon. A reaction with hydrogen bromide in strong acid results in rearrangement of the conjugated olefin with concomitant bromination on the new allylic methyl group (**20-4**). Treatment with sodium sulfite replaces halogen with sulfur to afford the sulfonic acid salt (**20-5**). The new functional group is then converted to the acid halide with phosphorus pentachloride. The reaction of that intermediate with *N*-methyl piperazine affords the remaining large moiety. The ester in (**20-6**) is then saponified to afford the free acid. Condensation of that last piece with the "dipeptide" (**19-7**) in the presence of DCC gives the renin antagonist **zankiren** (**20-7**) [25].
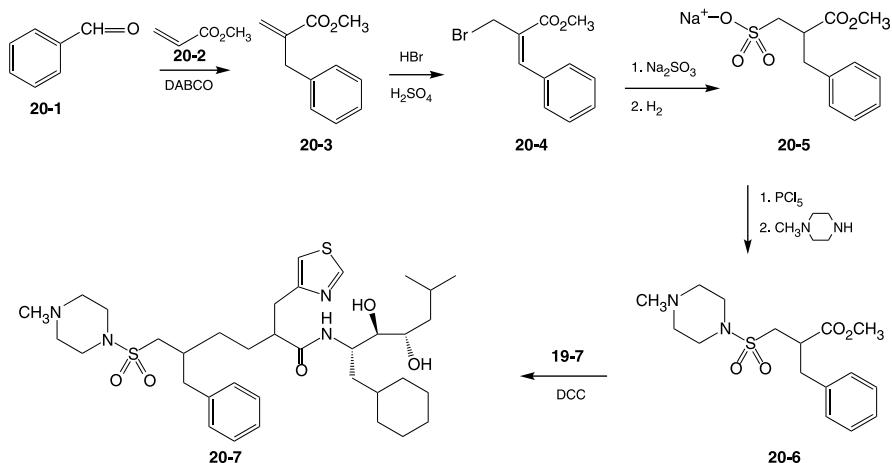
1.2.1.3. Antiviral Compounds

1.2.1.3.1. Human Immunodeficiency Virus. The functional simplicity of viruses combined with the fact that they require a living host for their replication has made them an unusually difficult therapeutic target. Human immunodeficiency virus (HIV), in common with most viruses, consists of a packet of genetic information encoded, in this case, in RNA and an outer protein coat. One of the final steps in viral replication involves synthesis of the coat peptide. Production of the coat peptide involves the scission of the initially produced, much larger protein by means of an aspartyl protease; a virus lacking the correct coat is not functional. The research that led to the HIV protease inhibitors detailed below represents a new era in drug development. The availability of a full three-dimensional structure of the protease, obtained by X-ray diffraction, made possible the use of computer-based modeling programs for designing inhibitors that best fit the target enzyme. This largely accounts for the fact that these inhibitors, which to some extent must mimic a polypeptide, include at the most only one of the naturally occurring amino acids.

The discovery that protease inhibitors were effective against HIV sparked intensive work in many laboratories on preparing proprietary compounds. Some nine discrete anti-HIV protease inhibitors have been approved by the Food and Drug Administration (FDA) as of this writing. The account that follows describes only a few from that large group.

The statine-like moiety in one of the first drugs, **saquinovir** (**23-8**), comprises a transition state mimic for the cleavage of phenylalanylprolyl and tyrosylprolyl sequences. Construction starts with the protection of the amino group of phenyl-alanine as its phthaloyl derivative (Phth) by reaction with phthalic anhydride; this is then converted to acid chloride. The chain is then extended by one carbon using a Friedel–Crafts-like reaction. The required reagent (**21-2**) is prepared by reaction of the enolate obtained from the *bis*-silyl ether (**21-3**) of glyoxylic acid and lithio

hexamethyldisilazane (LiHMDS) with trimethylsilyl chloride [26]. The uncatalyzed reaction of acid chloride (**21-1**) with (**21-2**) gives the chain extended product (**21-5**) directly on acidification; the first formed β-carbonyl compound (**21-4**) apparently decarboxylates spontaneously. The terminal alcohol is then protected as a tetra-hydropyranyl ether by adding it to dihydropyran; reduction of the ketone with sodium borohydride occurs enantioselectively due to the presence of the adjacent chiral center. Reaction with methanesulfonyl chloride then gives intermediate mesy-late (**21-6**), which is not isolated. The pyranyl ether is then removed by acid catalyzed exchange with ethanol to give (**21-7**). The alkoxide formed from the terminal hydroxyl in this last compound on treatment with potassium *tert*-butoxide internally displaces the adjacent mesylate to form epoxide (**21-8**), in which the configuration of the former alcohol carbon is inverted [27].
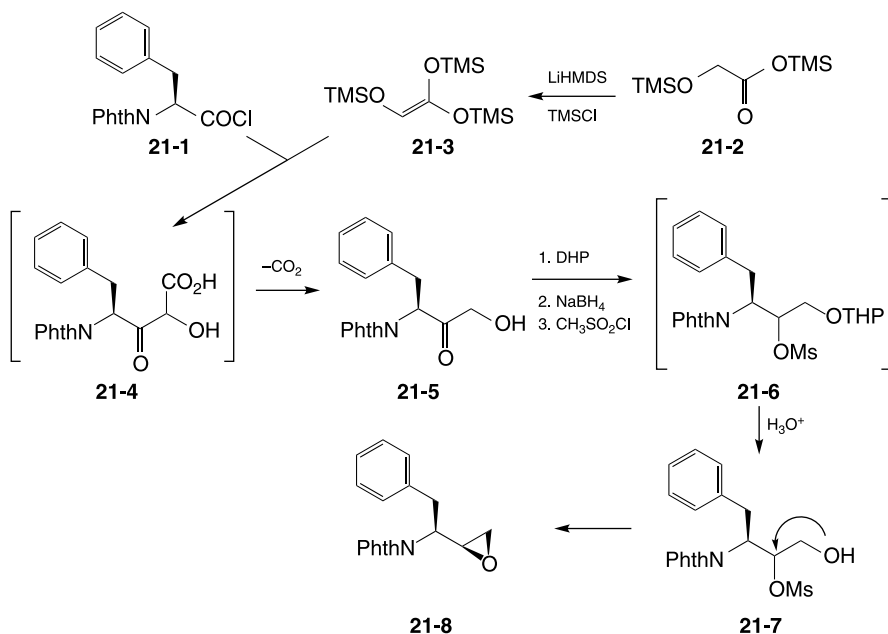
The other major fragment consists of a decahydroisoquinoline that may be viewed as a rigid analogue of an amino acid. Methanolysis of the adduct (**22-1**) from buta-diene and maleic anhydride in basic methanol gives the half-ester (**22-2**); the obligate *cis* stereochemistry of the adduct determines that of the future perhydroisoquinoline ring fusion. The half-acid is then resolved as its salt with *l*-ephedrine. The desired enantiomer is next converted to the acid chloride (**22-3**); hydrogenation under Rosenmund conditions, and palladium in charcoal in the presence of quinoline, lead to the aldehyde (**22-4**). The next step involves essentially adding methyl glyci-nate to the aldehyde group. Conversion of that compound to its benzal derivative (**22-5**) serves to remove the more acidic amino protons and at the same time activates the protons on the methylene group. Condensation of the lithium salt from that

compound with aldehyde (**22-4**) may be envisaged as first forming an adduct such as (**22-6**). The acidic workup serves to dehydrate the β-hydroxyester, to hydrolyze the Schiff base, and to cyclize the ester with the newly revealed amine, though not necessarily in that order. The first product isolated is in fact the lactam (**22-7**). Reaction with diborane in the presence of propylamine serves to reduce both the lactam and the olefin conjugated with the ester to afford (**22-8**). Displacement of the ester methoxyl by means of dibutylaluminum-*tert*-butylamide gives the decahydroquinoline (**22-9**) [27].
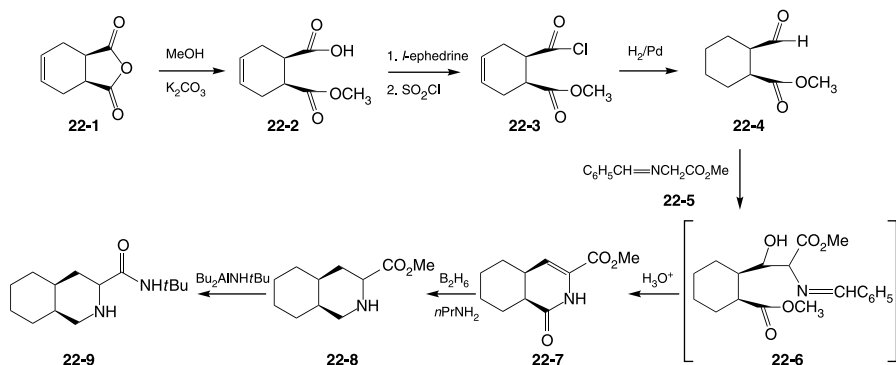
The last stage in this convergent synthesis comprises the connection of the individual units. The ring opening of epoxide (**21-8**) by the secondary amino group on perhydroisoquinoline (**22-9**) gives the alcohol (**23-1**). The phthaloyl protecting
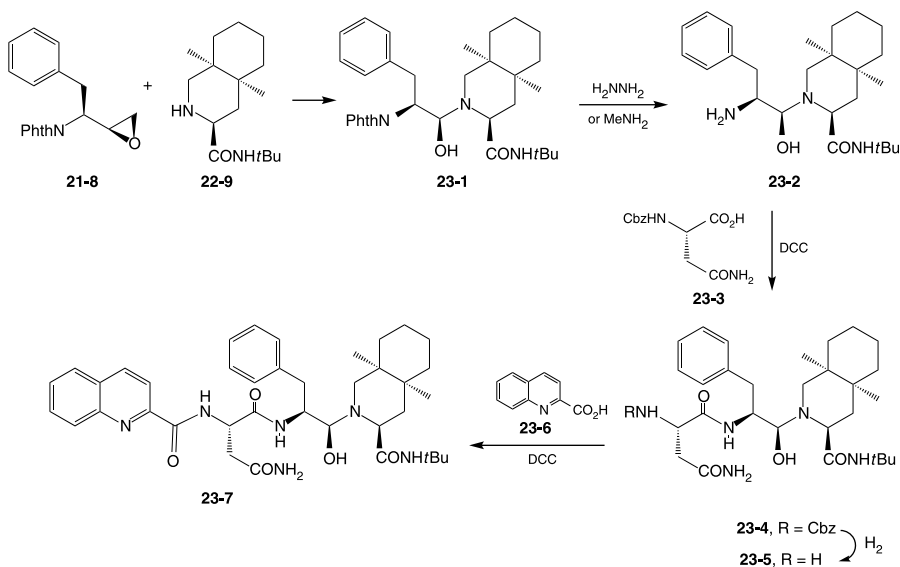
group is then removed by traditional treatment with hydrazine or, alternatively, with methylamine, the latter being more suitable to large scale work (**23-2**). The free amino group is then condensed with the Cbz derivative (**23-3**) of the monoamide from aspartic acid to give amide (**23-4**). Hydrogenation over palladium on charcoal reductively removes the benzyl group from the Cbz derivative; the unstable carbamic amide that remains decarboxylates to afford the amine (**23-5**). Condensation with quinoline-2-carboxylic acid (**23-6**) catalyzed by DCC forms the last amide bond [28]. There is thus obtained the HIV protease inhibitor **saquinovir** (**23-7**).

The HIV protease inhibitor **indinavir** (**24-11**) differs markedly in its structural components and is notable for the fact that it does not include a single natural α-amino acid [29]. Construction of this compound starts with reaction of resolved 1-amino-2-indanol with acetone to afford the cyclic carbinolamine derivative (**24-2**) that will act as a protecting group for both the amine and the alcohol. Acylation of this intermediate with hydrocinnamyl chloride (**24-1**) gives the amide (**24-3**). One of the key transformations in the sequence involves the alkylation of the carbanion obtained on treatment of (**24-3**) with LiHMDS with the toluenesulfonate derivative (**24-4**) from chiral glycidol. The enantioselective course of the alkylation reaction leading to (**24-5**) can be attributed to the proximity of the two chiral centers on the indan. In the other arm of the converging scheme, the catalytic reduction of the *tert*-butylamide (**24-6**) of pyrazine carboxylic acid gives the corresponding piperazine (**24-7**). This is then resolved as its camphorsulfonate salt. The amine at the 4 position is next selectively protected as its *tert*-butoxycarbonyl derivative (**24-8**) using BOC anhydride. The lesser steric bulk about that amino group as well as the possible hydrogen bonding of the amine at 1 with the adjacent carbonyl
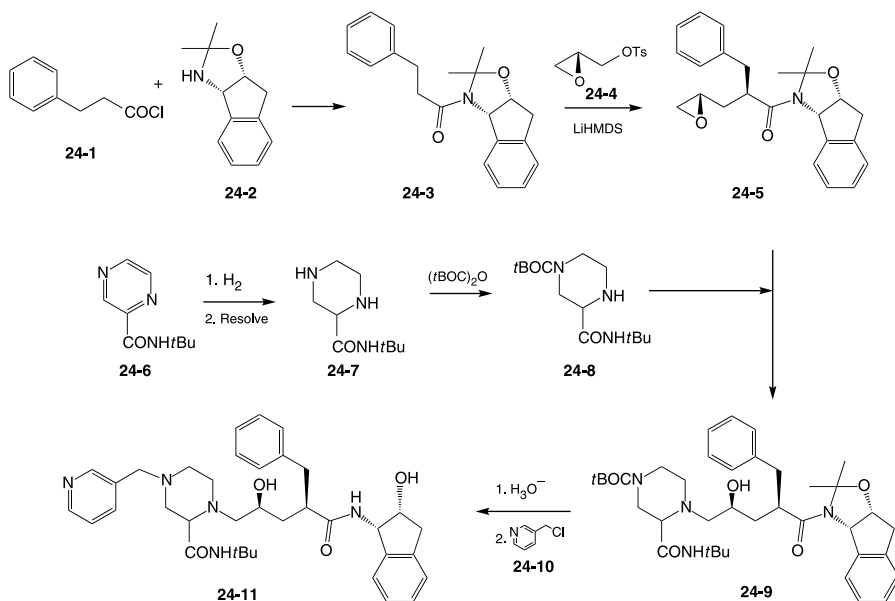
group contribute to the selectivity of this acylation step. Condensation of intermediate (**24-8**) with the large fragment (**24-5**) leads to an attack of the free amino group of the piperazine on the epoxide with consequent ring opening and formation of the alcohol (**24-9**); this reaction proceeds with the expected retention of configuration of the chiral center bearing the hydroxyl group. The *tert*-butoxycarbonyl protecting group is then removed by exposure of the intermediate to acid; the carbinolamine hydrolyzes under reaction conditions. Alkylation of the newly revealed piperazine nitrogen with 3-chloromethylpyridine (**24-10**) affords the protease inhibitor **indinavir** (**24-11**) [30].

One scheme for preparing a key intermediate for incorporating the statine-like fragment in the protease inhibitor **amprenvir** (**26-9**) begins with the chloromethyl ketone (**25-1**) derived from phenylalanine in which the amine is protected as a Cb group. Reduction of the carbonyl group by means of borohydride affords a mixture of aminoalcohols. The major *syn* isomer (**25-2**) is then isolated. Treatment of that compound with a base leads to the internal displacement of halogen and the formation of the epoxide (**25-3**) [31].
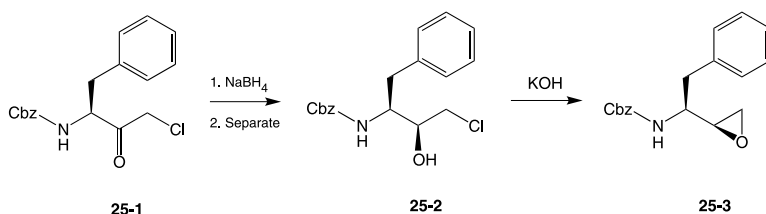
The corresponding analogue (**26-1**), in which the amine is protected as a *t*-butyloxycarbonyl function rather than Cbz, is used for preparing the HIV protease
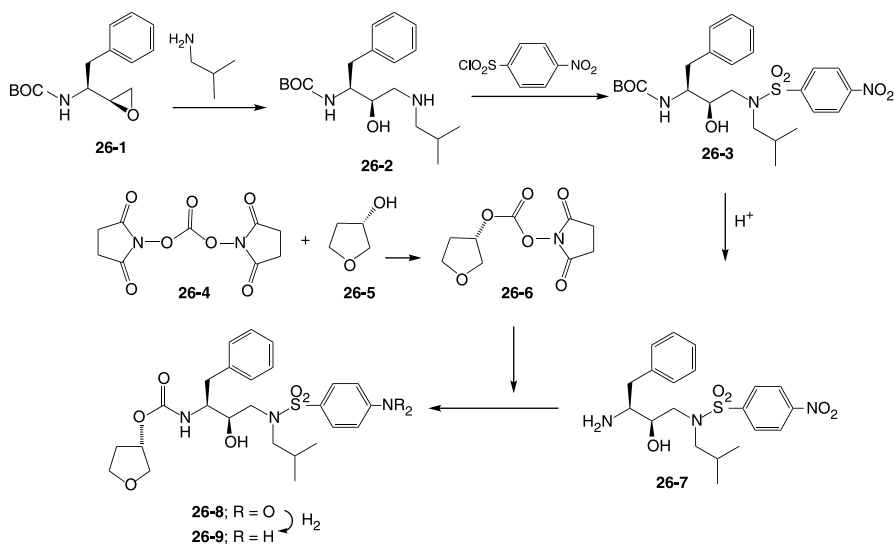
inhibitor **amprenavir** (**26-9**). Reaction of (**26-1**) with isobutyl amine leads to a ring opening of the oxirane and the formation of the aminoalcohol (**26-2**). The thus-formed secondary amine in the product is then converted to the sulfonamide (**26-3**) by treatment with *p*-nitrobenzenesulfonyl chloride. The BOC protecting group is then removed by exposure to acid, leading to primary amine (**26-7**). In a convergent scheme, chiral 3-hydroxytetrahydrofuran (**26-5**) is allowed to react with *bis*(*N*-sucinimidooxy)carbonate (**26-4**). The hydroxyl displaces one of the *N*-hydroxysuccinimide groups to afford the tetrahydrofuran derivative (**26-6**) equipped with a highly activated leaving group. Reaction of this intermediate with the amine (**26-7**) leads to the displacement of the remaining *N*-hydroxysuccinimide and the incorporation of the tetrahydrofuryl moiety as a urethane (**26-8**). Reduction of the nitro group then affords the protease inhibitor **amprenavir** (**26-9**) [32].

The protease inhibitor **atazanivir** includes some significant structural differences from the preceding examples, though it shares a similar central aminoalcohol sequence that is presumably the pharmacophore. Construction of one end of the molecule begins with the protection of the carbonyl function in *p*-bromobenzaldehyde (**27-1**) as its methyl acetal (**27-2**) by treatment with methanol in the presence of acid. The reaction of that intermediate with the Grignard reagent from 4-bromopyridine leads to an unusual displacement of bromine from the protected benzaldehyde and the formation of the coupling product. Mild aqueous acid restores the aldehyde function to afford (**27-3**). This is then condensed with *t*-butyloxycarbonyl hydrazine
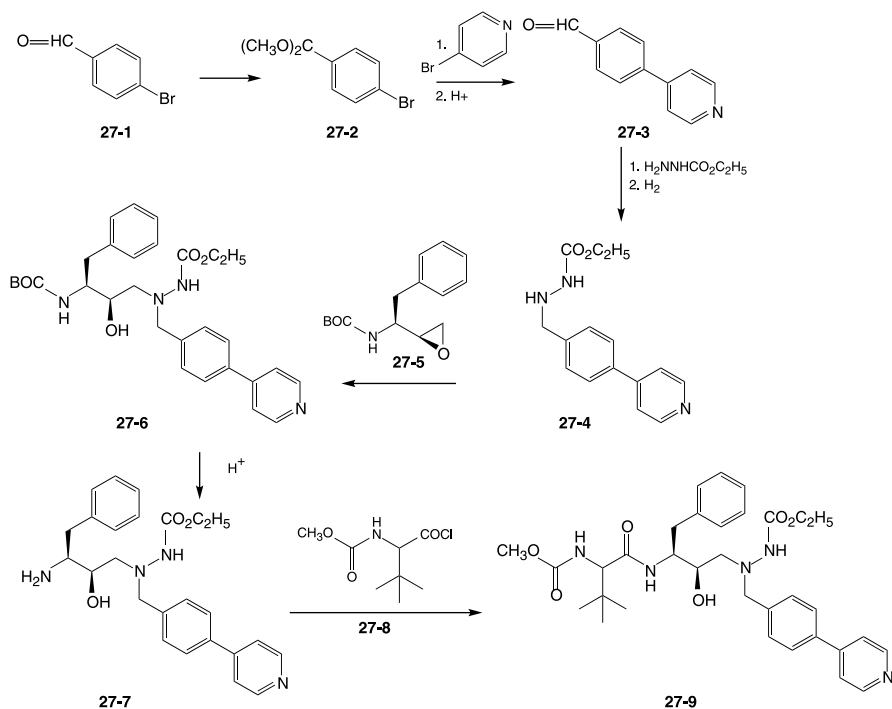
to form the respective hydrazone. Reduction of the imine function leads to the substituted hydrazine (**27-4**). The reaction of this last intermediate with the amino-epoxide (**26-1**), also used for amprenavir, results in an oxirane opening by attacking the basic nitrogen in hydrazine (**27-4**) and the consequent formation of the addition product (**27-6**). The BOC protecting group is then removed by treatment with acid. The final step comprises the acylation of the free primary amine in (**27-7**) with the acid chloride from the *O*-methyl urethane (**27-8**). This is a protected version of an unnatural α-aminoacid that can be viewed as valine with an additional methyl group on what had been the side chain secondary carbon atom. There is thus obtained the protease inhibitor **atazanavir** [33] (**27-9**).

1.2.1.3.2. Human Rhinovirus. Human rhinoviruses are one of the most frequent causes of the affliction that accompanies cooling weather, the common cold. These viruses, too, consist of a small strand of RNA enveloped in a peptide coat. Fresh virions in this case also depend on the excision of that peptide from the larger initially produced protein. The statine-based HIV drugs act by occupying the scission site of the protease enzyme and consequently preventing access by the HIV-related substrate. That binding is, however, reversible in the absence of the formation of a covalent bond between the drug and the enzyme. A different strategy was employed in the research that led to the rhinovirus protease inhibitor **rupinavir** (**29-5**). The molecule as a whole is again designed to fit the protease enzyme, as in the case of the anti-HIV compounds. In contrast to the latter, however, this agent incorporates a moiety that will form a covalent bond with the enzyme, in effect inactivating it with finality.

The main part of the somewhat lengthy convergent synthesis consists of the construction of a Michael acceptor for a thiol group on a cysteine residue known to be present at the active site of viral proteiase. The preparation of that key fragment starts with the protected form of chiral 3-amino-4-hydroxybutyric acid (**28-1**); note that the oxazolidine protecting group simply comprises a cyclic hemiaminal of the aminoalcohol with acetone. The first step involves the incorporation of a chiral auxiliary to guide the introduction of an additional carbon atom. The carboxylic acid is thus converted to the corresponding acid chloride and is then reacted with the S isomer of the by-now classic oxazolidinone (**28-2**) to give the derivative (**28-3**). Alkylation of the enolate from (**28-3**) with allyl iodide gives the corresponding allyl derivative (**28-4**) as a single enantiomer. The double bond is then cleaved with ozone; reductive workup of the ozonide affords the aldehyde (**28-5**). Reductive amination of the carbonyl group with 2,6-dimethoxybenzylamine in the presence of cyanoborohydride proceeds to the corresponding amine (**28-6**). This last step in effect introduces a protected primary amino group at that position. The chiral auxiliary grouping is next removed by mild hydrolysis. The initially formed amino acid (**28-7**) then cyclizes to give the five-membered lactam (**28-8**). Treatment under stronger hydrolytic conditions subsequently serves to open the cyclic hemiaminal grouping to reveal the free aminoalcohol (**28-9**). Swern-type oxidation of the terminal hydroxyl group in this last product affords an intermediate (**28-10**) that now incorporates the aldehyde group required for building the Michael acceptor function. Thus the reaction of

that compound with the ylide from ethyl 2-diethoxyphosphonoacetate adds two carbon atoms and gives the acrylic ester (**28-11**).
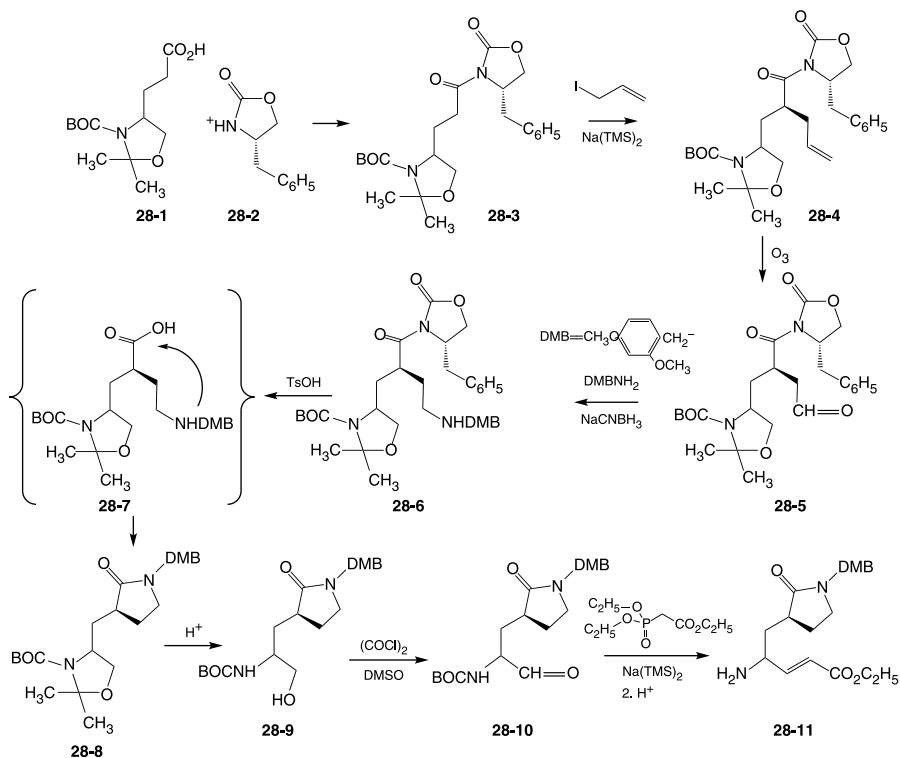
The remaining part of the target molecule is prepared by the condensation of *N*-carbobenzyloxyleucine with *p*-fluorophenylalanine to give the protected dipeptide
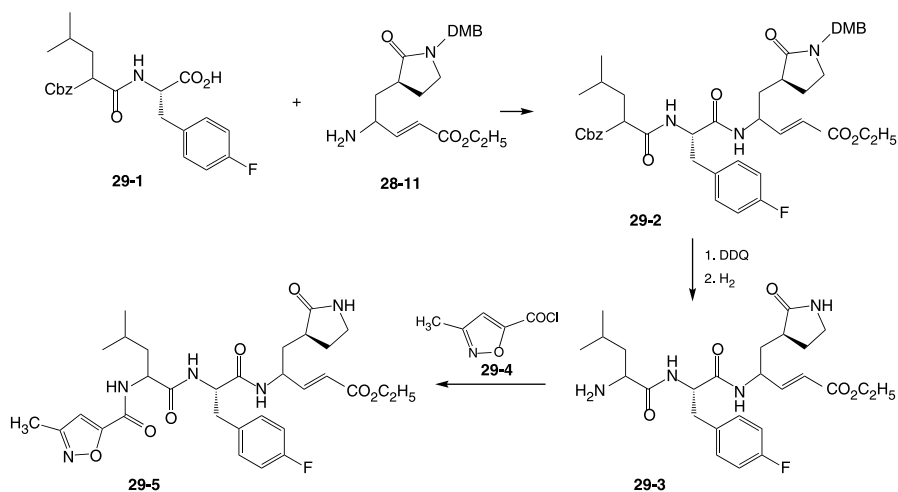
(**29-1**). Condensation of that intermediate with the Michael acceptor fragment (**28-11**) under standard peptide-forming conditions leads to the dipetide-like compound (**29-2**). The reaction of that with dichlorodicyanoquinone (DDQ) leads to the unmasking of the amide group by oxidative loss of the DMB protecting group; hydrogenation then removes the carbobenzyloxy protecting group on the terminal amine (**29-3**). Acylation of that function with isoxazole (**29-4**) finally affords the rhinovirus protease inhibitor **rupinavir** (**29-5**) [34].

1.2.2. Fibrinogen Receptor Antagonists

Formation of the clots that seal off broken blood vessels begins with the aggregation of platelets at the site of injury. This event sets off the long cascade that leads to the formation of fibrin. Inappropriate aggregation of platelets leads to the formation of clots that lead to thromboses or even strokes. The aggregation of platelets depends on the binding of fibrinogen to specific sites on platelet membranes. The presence of two arginine–glycine–aspartic sequences in the structure of fibrinogen has led to the development of several antagonists, parts of whose structures mimic that sequence. No fewer than eight fibrinogen antagonists have been granted USAN as of this writing.

   The key starting material of one of the first antagonists, **argatroban** (**30-6**), comprises a derivative of arginine itself in which the amine is protected as its *tert*-butoxycarbonyl derivative and an *N*-nitro group moderates the basic nature of the guanidine group (**30-2**). That intermediate is first condensed with the piperidine
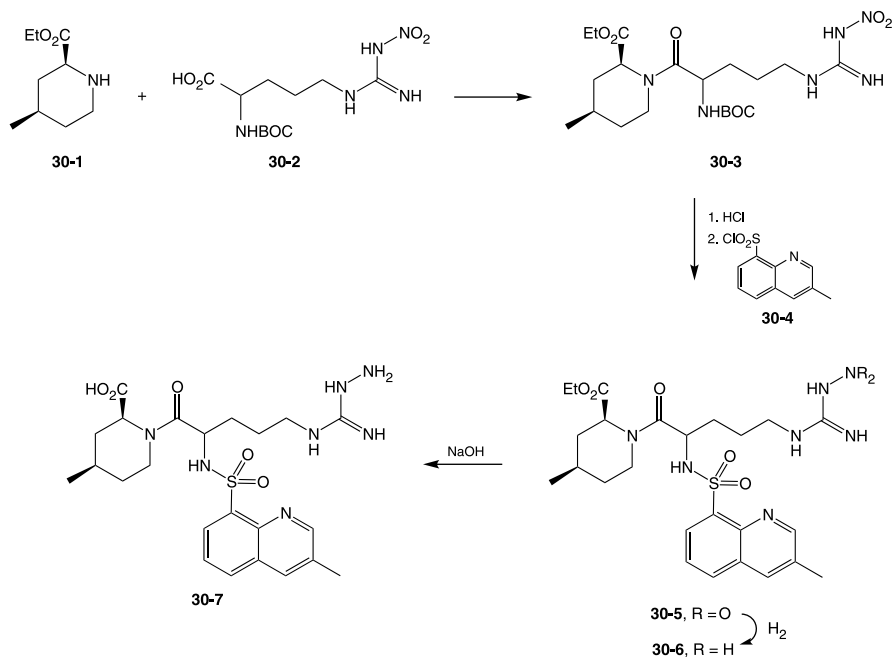
(**30-1**). The BOC protecting group is the removed by treatment with acid. The newly revealed primary amine is next acylated using quinoline sulfonyl chloride (**30-4**). Catalytic hydrogenation of the product (**30-5**) from this last reaction serves to reduce the nitro group to form an *N*-amino guanidine (**30-6**). Saponification of the ester completes the synthesis of **argatroban** (**30-7**) [35].

A somewhat more complex compound features a guanidine function in which one of the nitrogen atoms forms part of a piperidine ring. Construction of that function begins with catalytic hydrogenation on 3-aminomethylpyridine to give the corresponding piperidine; that product is then resolved by way of its tartrate salt to afford (**31-2**) as a single enantiomer. The reaction of (**31-2**) with methyl acetoacetate (**31-1**) discriminates between the primary and secondary amino groups in the compound since the former more readily form an enamine with the β-ketoester. The reaction of the thus-protected intermediate (**31-3**) with triazolo amidine (**31-4**) leads to the transfer of the amidine to the more basic amine on the piperidine and the formation of guanidine (**31-5**). Trreatment of that product with aqueous acid leads to hydrolysis of the enamine to afford the synthon (**31-6**).
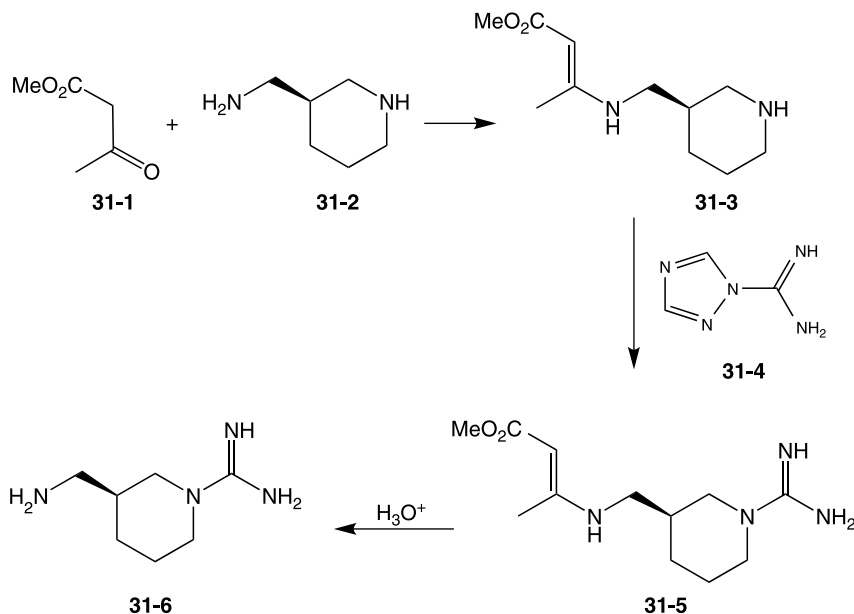
The naphthyl sulfonamide derivative (**32-1**) of glutamic acid comprises the starting material for the other part of **napsagatran**. The reaction of the sulfonamide with formaldehyde in the presence of acid probably starts by the formation of a carbinolmine by addition to amide nitrogen. This intermediate cyclizes to oxazolidine (**32-2**) under reaction conditions. This newly formed ring activates the ring carbonyl ring toward displacement by providing a good leaving group. Reaction of that compound with *N*-cyclopropyl glycine, itself obtained from displacement by bromine in ethyl

bromoacetate by cyclopropyl amine, leads to the amide (**32-3**). The carbinolamine that results from the ring opening reverts to the sulfonamide under reaction conditions. Condensation of the carboxylic acid in (**32-3**) with primary amine (**33-4**) followed by saponification of the terminal ester afford the fibrinogen antagonist **napsagatran** (**32-5**) [36].
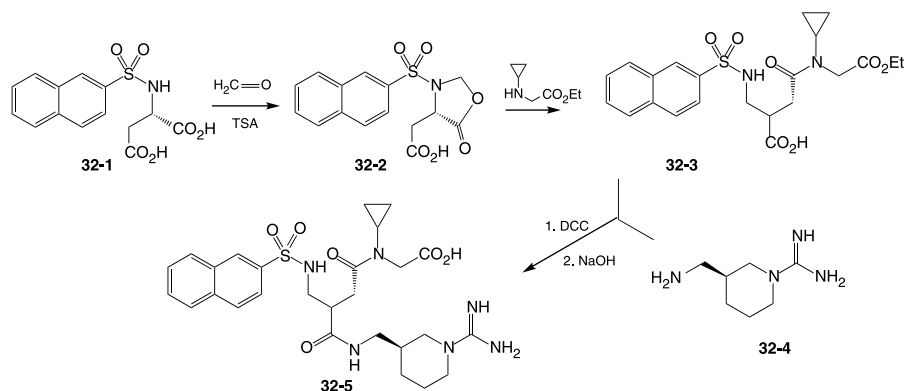
The observation that activity is retained when the guanidine is replaced by an amidine group points to the considerable degree of freedom that exists in this series for receptor recognition. This also applies for the rest of the chain since naturally occurring amino acids can be replaced by other groups. The resulting compounds should also be less likely to be metabolized by proteolytic enzymes
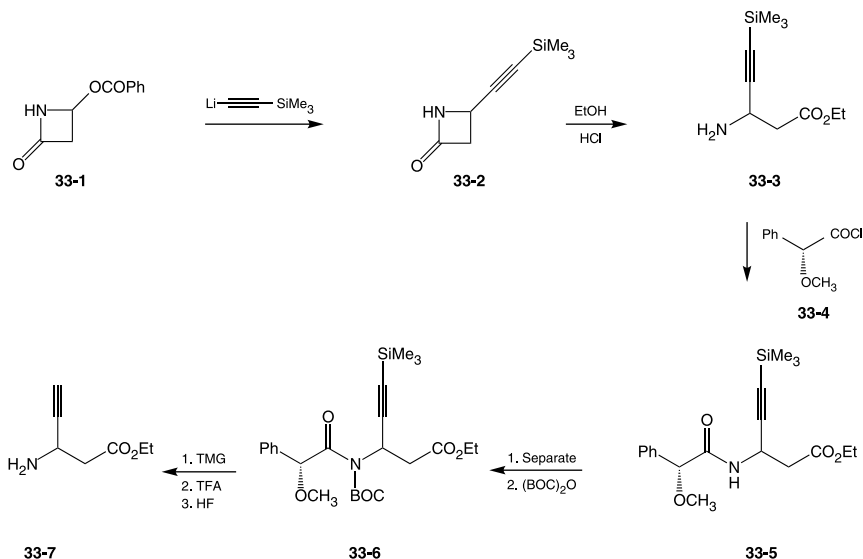
TMG = tetramethylgunidine

than the peptide based drugs. The synthesis of **xemilofiban** (**34-4**) starts with the preparation of an "unnatural" β amino acid. Displacement of the benzoate ester in azetidone (**33-1**) by the lithio anion from trimethylsilyl acetylene affords the C-alkyne derivative (**33-2**). The azetidone may exist as its enolate under reaction conditions, protecting the ring carbonyl group from attack by the acetylide. Fisher esterification in ethanol opens the ring to give the ethyl glycinate (**33-3**) as a mixture of enantiomers. This is then acylated with chiral *O*-methyl mandelic chloride. The resulting mixture of diastereomers is then separated by chromatography. The desired isomer (**33-5**) is next converted to its *tert*-butoxycarbonyl derivative by exposure to BOC anhydride. Tetramethylguanidine then serves to cleave the amide bond, releasing the chiral auxiliary mandelate. Succesive reaction with trifluoroacetic acid and hydrogen fluoride removes the remaining protective group to afford the β-amino ester (**33-7**) as a single enantiomer.

In a convergent sequence amidine (**34-1**) is allowed to react with succinic anhydride to afford the amide (**34-2**). The resulting acid is then condensed with the amino acid (**33-7**). The fibrinogen **xemilofiban** (**34-3**) is thus obtained [37].
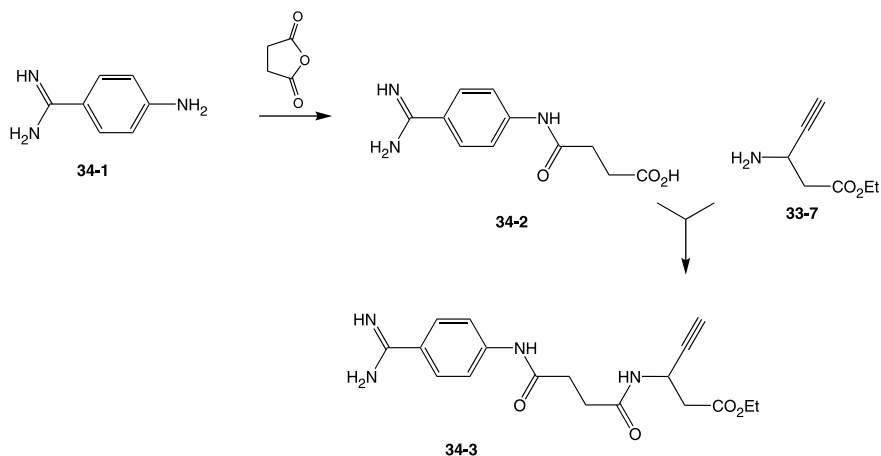
The synthesis of yet another fibrinogen antagonist starts with the hydrogenation of phenylglycine BOC amide (**35-1**) to the corresponding cyclohexyl derivative (**35-2**). The free carboxyl group is then coupled with the azetidine (**35-3**) to afford the amide (**35-4**). Saponification with lithium hydroxide then gives the free acid (**35-5**). The carboxyl group in that product is then coupled with the benzylamine (**35-6**), in which the amidine group at the *para* position is protected as the benzyloxycarbonyl derivative to give intermediate (**35-7**). The protecting group on the terminal amino group is then removed by hydrolysis with acid (**35-8**). The primary amine in this last intermediate is then alkylated with benzyl bromoacetate. Hydrogenolysis removes the protecting groups on the terminal functions in this molecule to afford **melagartan** (**35-9**) [38].
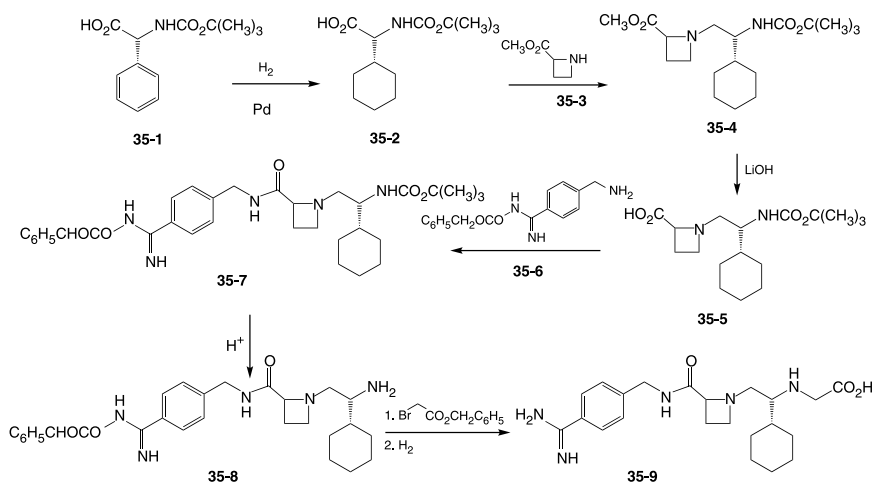
1.2.3. Antitumor Peptidomimetic

The microskeleton of cells consists of structures called microtubules that consist of polymers of the peptide tubulin. During cell division these filaments pull apart the nascent newly formed pair of nuclei. Compounds that interfere with tubulin function and thus block this process, such as, for example, the vinca alkaloid drugs vincristine and vinblastine, block the self-assembly of tubulin into those filaments. Paclitaxel, more familiarly known as Taxol®, on the other hand stabilizes tubulin and in effect freezes cells into mid-division. Screening of marine natural products uncovered the cytotoxic tripeptide-like compound hemiasterlin that owes its activity to the inhibition of tubulin formation. A synthetic program based on that led to the identification of **taltobulin (36-12)**. The conjugated unsaturated ester in this molecule suggests that it may act as a nonreversible inhibitor by binding to its site by covalent bonds.

One arm of the convergent synthesis begins with the construction of that acrylate-containing moiety. Thus, condensation of the BOC protected α-aminoaldehyle (**36-1**) derived from valine with the cabethoxymethylene phosporane (**36-2**) gives the corresponding chain extended amino ester (**36-3**). Exposure to acid serves to remove the protecting group to reveal the primary amine (**36-4**). Condensation of that intermediate with the tertiary butyl-substituted aminoacid (**36-5**) leads to the protected amide (**36-6**); the BOC group in this is again removed with acid to unmask the primary amino group in (**36-7**). Construction of the other major fragment involves, first, the addition of a pair of methyl groups to the benzylic position of pyruvate (**36-8**). This transform is accomplished under surprisingly mild conditions by simply treating the keto-acid with methyl iodide in the presence of hydroxide. Treatment of the product (**36-9**) with methylamine and diborane results in reductive amination of the carbonyl group and thus the formation of α-aminoacid (**36-10**) as a mixture of the two isomers. Condensation of that with the dipeptide-like moiety (**36-7**) under standard peptide-forming conditions gives the amide (**36-11**) as a mixture of diastereomers. The

isomers are then separated by chromatography; saponification of the terminal ester function of the desired *SSS* isomer affords the antitumor agent **taltobulin** (**36-12**) [39] .
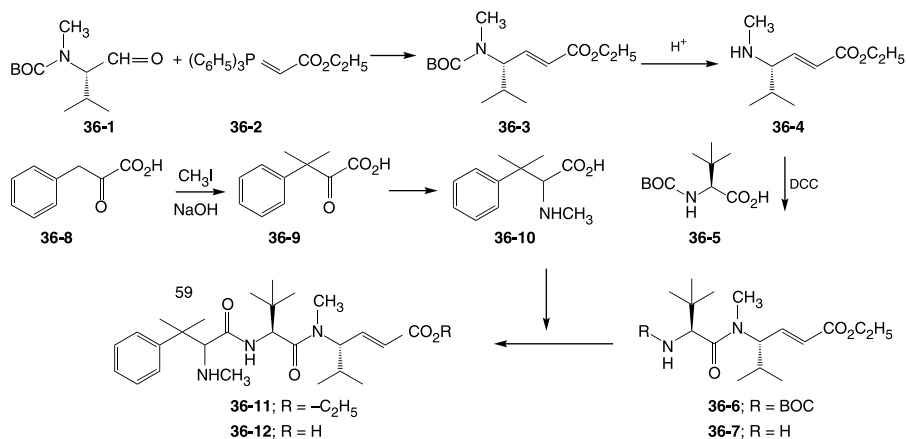

1.3. RETINOIDS

Vitamin A consists of a mixture of two polyene diterpenes, retinol and its biologically active oxidation product, retinal, shown as its *trans* isomer (**37-1**). Retinal forms a crucial link in vision; light-induced isomerization of the double bond adjacent to the carbonyl, conjugated with vision proteins as a Schiff base, from *cis* to *trans* plays a key role in the transduction of light to visual perception. The metabolite from oxidation of retinal, retinoic acid (**37-2**), has potent biological activity in its own right. The compound is a ligand for receptors involved in epithelial differentiation. All-*trans* retinoic acid, under the USAN **tretinoin**, has, as a result of that activity, found clinical use in the treatment of skin diseases such as acne. Considerable research has been prompted by data suggesting that the agent may have an effect on cancer progression.

37-1
Retinal

37-2
Retinoic Acid
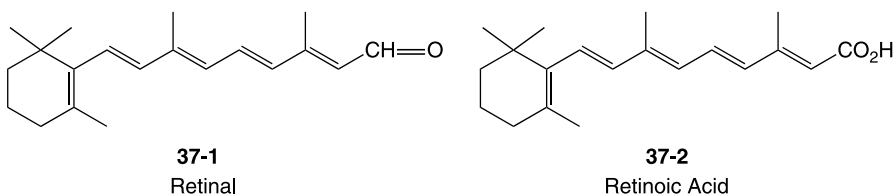
   The majority of published syntheses of **tretinoin** start with readily available β-ionone (**38-1**), a compound that already incorporates the highly substituted cyclohexene ring as well as four of the side chain atoms. Condensation with the carbanion from acetonitrile followed by dehydration of the initially formed carbinol gives the intermediate (**38-2**). Reduction of the cyano group by diisobutylaluminum hydride leads to the

corresponding imine; this hydrolyzes to aldehyde (**38-3**) during the acid workup [40]. Base-catalyzed aldol condensation of that aldehyde with β-methylglutaconic anhydride (**38-4**) involves condensation with the activated methylene group of the anhydride and leads to the product (**38-5**) in which the remainder of the side chain has been added. The anhydride is then hydrolyzed to the vinylogous β-dicarboxylic acid (**38-6**). The superfluous carboxyl group is removed by heating the compound in quinoline in the presence of copper to afford acid (**38-7**). The terminal double bond is then isomerized by any of several methods to give **tretinoin** (**38-8**) [41].
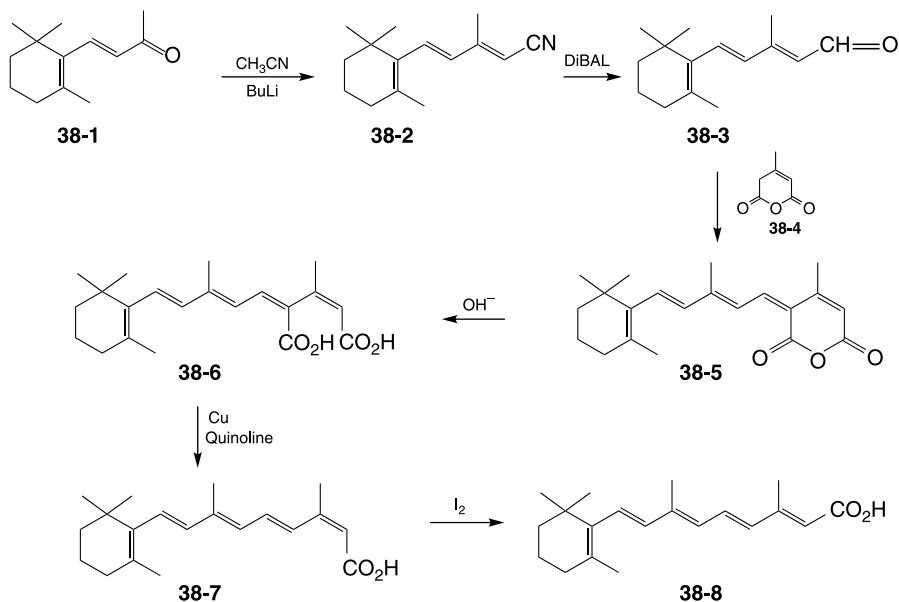
The closely related 9-*cis* isomer of retinoic acid binds to a different set of receptors involved in skin cell growth and has been found to control the proliferation of some cancer cells. The drug is thus indicated for topical use in controlling the spread of Kaposi sarcoma lesions. Reduction of the ester group in compound (**39-1**), which incorporates the requisite future 9-*cis* linkage, with lithium aluminum hydride leads to the corresponding alcohol. This is then oxidized to aldehyde (**38-2**) by means of manganese dioxide. Condensation of the carbonyl group with the ylide derived by treatment of the complex phosphonate (**38-3**) adds the rest of the
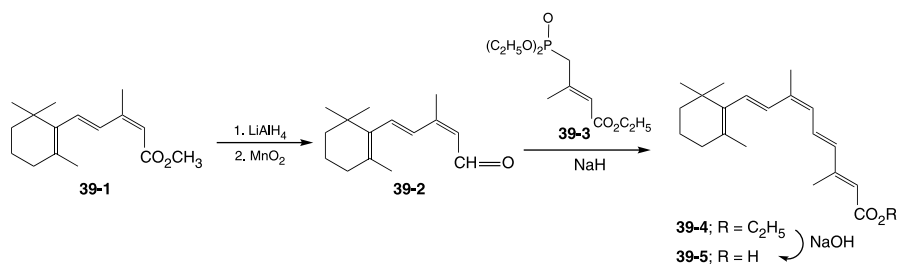
carbon skeleton (**39-4**). Saponification of the ester then gives the corresponding acid, **alitretinoin** (**39-5**) [42].

Replacement of the cylohexene ring by an aromatic moiety is interestingly still consistent with retinoid-type activity. Construction of this analogue starts by reaction of 2,3,5-trimethyl anisole (**40-1**) with acetylene (**40-2**), itself obtainable from acetylene and methylvinyl ketone, with a strong Lewis acid under Friedel–Crafts conditions. The ambident carbocation from (**40-2**), where the charge is smeared over the entire chain, reacts with the aromatic ring at the end of the acetylene moiety. The alkylated intermediate then adds back the hydroxyl at the terminal position to give the terpene-like intermediate (**40-3**); the resulting allylic alcohol is then converted to its bromide (**40-4**). Displacement of halogen by means of triphenylphosphine leads to phosphonium salt (**40-5**). Wittig condensation of the ylide from this last intermediate with the half-aldehyde derivative of α-methylfumaric ester (**40-6**) adds the remainder of the retinoid side chain. Saponification of the ester then affords **etretinate** (**40-7**) [43].
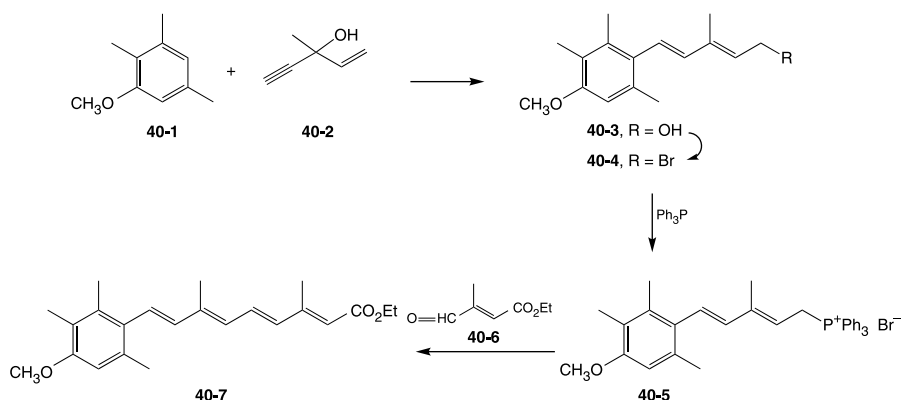
Activity is largely retained in a compound in which one of the terminal double bonds in the side chain of **tretinoin** is replaced by an aromatic ring. The key reaction in the construction of this compound consists in Wittig condensation of the ylide from
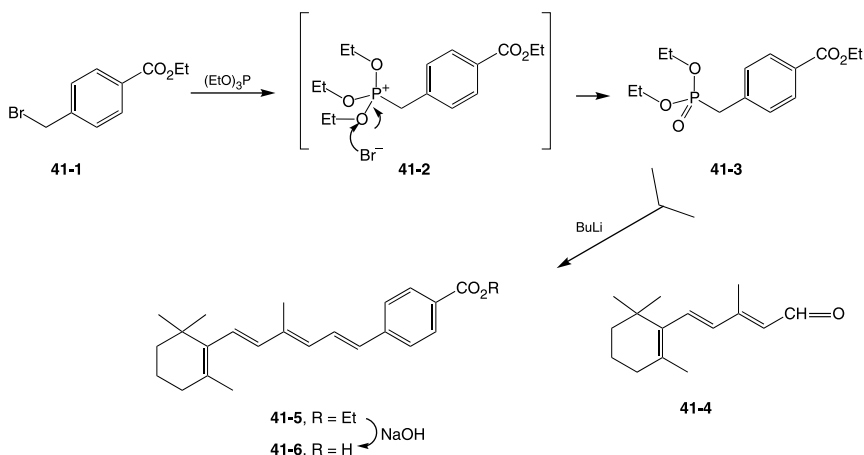
phosphonate (**41-3**) with the chain extended aldehyde (**38-3**) used in the synthesis of **tretinoin** itself. The Arbuzov rearrangement provides ready access to the phosphonate. Reaction of ethyl *para*-bromomethylbenzoate (**41-1**) with triethyl phosphite probably proceeds by initial displacement of halogen by phosphorus to give a transient intermediate charged species such as (**41-2**). Displacement of one of the ethyl groups on phosphorus by a bromide ion from the first displacement followed by bond reorganization leads to phosphonate (**41-3**) and ethyl bromide as a by-product. Reaction of the ylide from that product with aldehyde (**38-3**) affords the extended polyene (**40-5**). Saponification then yields **pelretin** (**41-6**) [44].

1.4. A MISCELLANEOUS DRUG

Fermentation broths have proven to be a very rich source for leads for antibiotics, a circumstance helped significantly by bioassays against bacteria that are sensitive to very low levels of active agents in the broths. The development of high turnover in *in vitro* screens against other endpoints provided leads for compounds in other therapeutic targets. The original lead for the enormously popular statins came from just this sort of program. Another program turned up a compound that inhibited pancrealipase, the enzyme responsible for the hydrolysis of dietary triglycerides to circulating fatty acids. The drug that came out of this program, **orlistat** (**43-8**), known in the press as a "fat blocker," offers dieters the ability to control caloric intake without foregoing fatty delicacies.

The structure of this agent in essence comprises a propiolactone that bears two long fatty acid-like side chains. Construction of one of the side chains in this somewhat lengthy synthesis begins with the cyclohexanone acetal of L-mallic acid (**42-1**). The carboxylic acid is first reduced to the carbinol by means of diborane, and that is then protected as its *tert*-butyldimethylsilyl ether (**42-2**). The acetal ring is then opened by means of sodium methoxide in methanol (**42-3**). The resulting ester is then reduced, and the resulting hydroxyl is converted to a leaving group by reaction
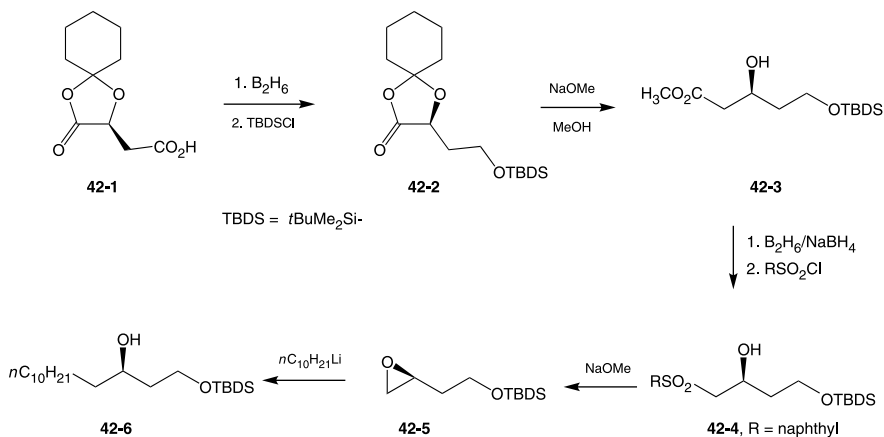
with naphthylsulfonyl chloride (**42-4**). Treatment with a strong base leads to internal displacement and thus the formation of the oxirane (**42-5**). The ring is then opened with the lithium reagent from the exchange of *n*-bromodecane with butyllithium to afford the long chain product (**42-6**) [42].

Addition of the second part of the molecule starts by first protecting the free hydroxyl group as its benzyl ether by exchange with *O*-benzyliminitrifloroacetamide. The silyl protecting group on the other hydroxyl is then removed by means of hydrogen fluoride. Swern oxidation then converts that to an aldehyde group (**43-1**). the titanium tetrachloride catalyzed addition of a carbocation to the aldehyde group serves to add the second fatty side chain. Thus the addition of the ambient carbocation from the allylic silyl reagent (**43-2**) in the presence of *bis*-cyclopentyldienyl-titanium dichloride gives the condensation product (**43-3**). Asymmetric induction by the adjacent chiral ether leads to the stereoselective formation of the new chiral center. Ozonization of the terminal olefin followed by an oxidative workup leads to the loss of the two terminal carbon atoms and the formation of the carboxylic acid (**43-4**). Treatment of the hydroxyl acid with benzenesulfonyl chloride in pyridine leads those functional groups to cyclize to the propiolactone (**43-5**), likely though the intermediacy of the sulfonate. The configuration of the hexyl side chain is next inverted to match that of the natural product via its enolate by treatment with a strong base. Hydrogenolysis of the benzyl ether affords the intermediate (**43-6**). The last fragment, formyl leucine (**43-7**), is added by means of a version of the Mitsonobu reaction. Thus the reaction of (**43-6**) with the acid in the presence of diethyldiazo dicarboxylate (DEAD) and triphenyl phosphine leads to the ester (**43-8**) and thus **orlistat** [45]. The inversion of configuration at oxygen indicates that this last reaction involves SN$_2$-like displacement rather than esterification.
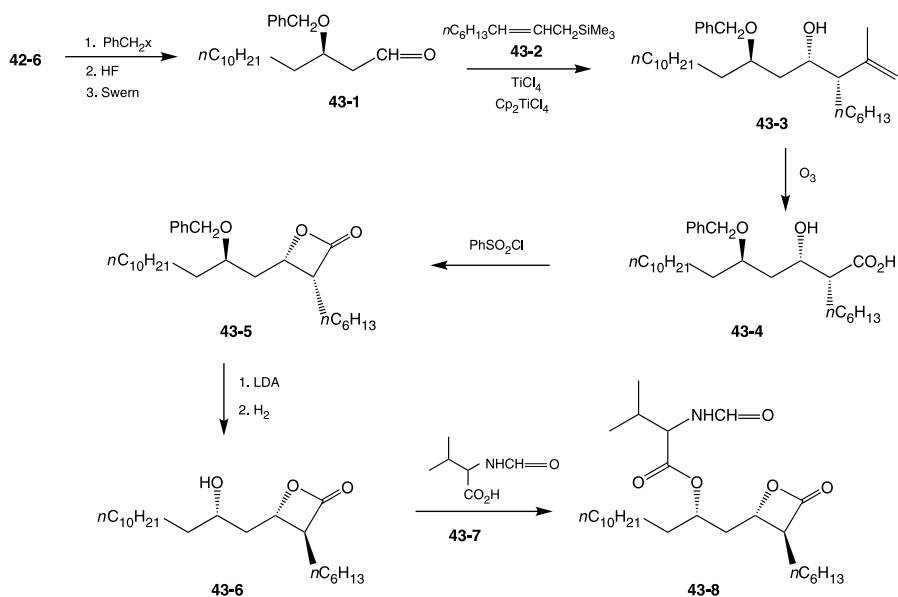
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CHAPTER 2

# DRUGS BASED ON A SUBSTITUTED BENZENE RING

Benzene rings as well as other aromatic systems abound among compounds used as therapeutic agents. The 60-odd drugs described in this chapter represent a very small sample of the hundreds of agents that are centered on substituted benzene rings. These rings play manifold functions in drugs, ranging from simply providing simple steric bulk to forming an integral part of the pharmacophore. Most, but not all, of the drugs discussed in this chapter fall into the latter category and have been chosen for inclusion for their illustrative value.

2.1. ARYLETHANOLAMINES

One of the most reliable sources for leads for new drugs consists of the endogenous compounds that act as messengers for various vital functions. **Epinephine** (**1-1**), also known as **adrenalin**, and its *N*-demethyl derivative **norepinephrine** (**1-2**), two closely related arylethanolamines that play a key role in homeostasis, were isolated and characterized structurally in the mid-1930s. It was already recognized at the time that these two agents are intimately associated with the sympathetic branch of the involuntary, sometimes referred to as the autonomic nervous system. These compounds, which, among other functions, transmit nerve signals across synapses in this system, play a key role in regulating blood pressure, heart rate, and constriction or dilation of bronchioles. The central role that adrenalin plays in this branch of the nervous system leads to its name as the adrenergic system.

1-1
Epinephrine

1-2
Norepinephrine
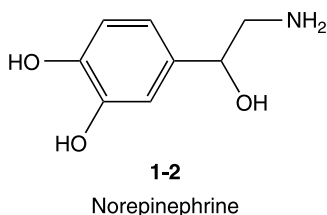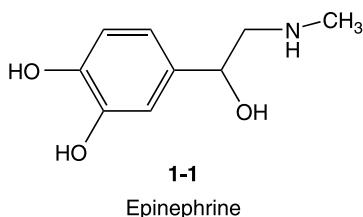
Epinephrine is often one of the first drugs used in treating trauma because of its cardiostimulant and bronchodilating actions. Simple replacement of the methyl group on nitrogen by isopropyl gives **isoproterenol** (**2-3**), a drug with a longer duration of action. Each of these drugs is available in racemic form by a relatively short, straight-forward synthesis. Friedel–Crafts acylation of catechol with chloroacetyl chloride leads to the chloroketone (**2-1**). Displacement of halogen with isopropylamine gives aminoketone (**2-2**); hydrogenation over platinum reduces the carbonyl group to give racemic **isproterenol** (**2-3**). The same sequence using methylamine leads to **epinephrine**, and resolution of this last as its tartrate salt gives *l*-**epinephrine** (**1-1**) identical to the natural product [1].
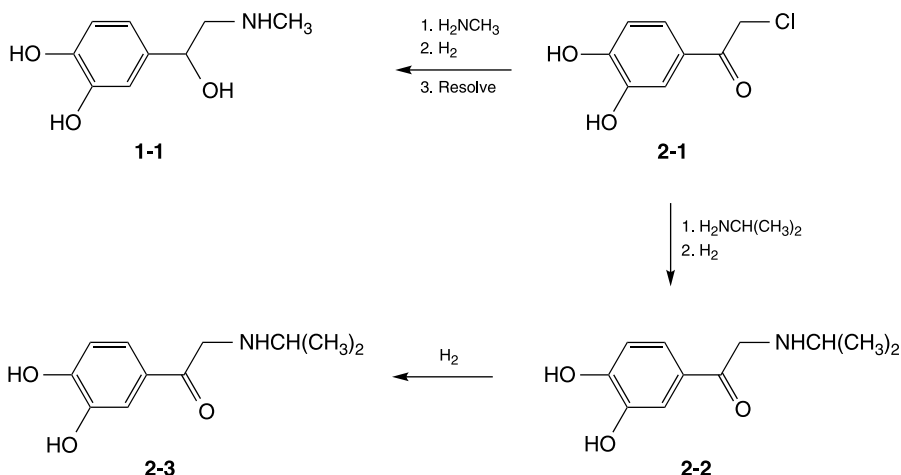
The isomer of (**2-3**) in which both phenolic hydroxyl groups occupy the *meta* position, **metaproterenol** (**3-5**), retains the bronchodilating activity of the isoproterenonol. The synthesis begins with treatment of substituted acetophenone (**3-1**) with selenium dioxide; the methyl group is thus oxidized to the corresponding aldehyde to give glyoxal (**3-2**). Reductive amination with isopropylamine can be envisaged to proceed first through the imine (**3-3**). Hydrogen then reduces that function to the secondary amine. The carbonyl group is reduced in the process to give aminoalcohol (**3-4**). The phenolic methyl ethers are then cleaved by means of hydrogen bromide to give **metaproterenol** (**3-5**) [2].
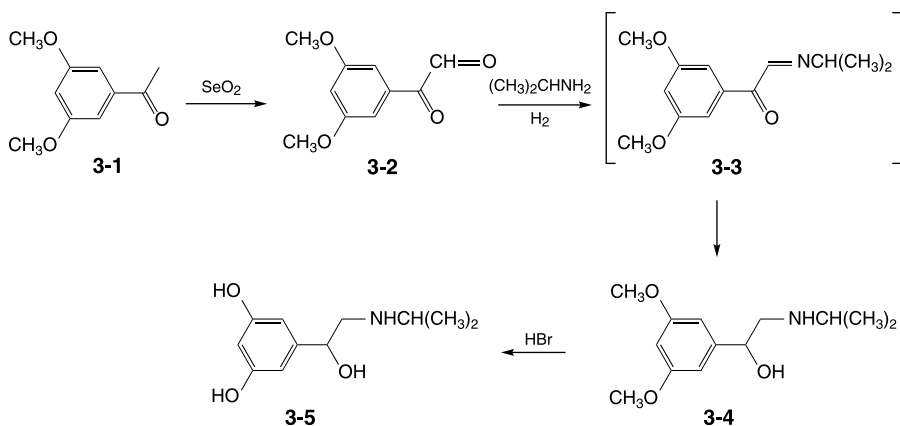
The adrenergic nervous system is itself divided into two broad categories, denoted as the α and β branches. Drugs such as **metaproteronol** and **deterenol**, a congener of **isoproterenol** lacking the *meta* hydroxyl group, act largely as β-adrenergic agonists. The fact that the proton in a sulfonylanilide should have a pK in the same range as a phenol encouraged the preparation of the deterenol congener **sotalol** (**4-4**). It is of note that though this compound interacts with β-adrenergic receptors, it does so as an antagonist. This compound was in fact one of the first β-blockers. One of several routes to this compound starts with the reduction of readily available *para*-nitroacetophenone (**4-1**) to the correspond-ing aniline (**4-2**) by a method specific to nitro groups such as iron and hydrochloric acid. Reaction with methanesulfonyl chloride gives the sulfonanilide (**4-3**). This intermediate is then carried on to **sotalol** (**4-4**) by the same series of reactions used to prepare **isoproterenol**.
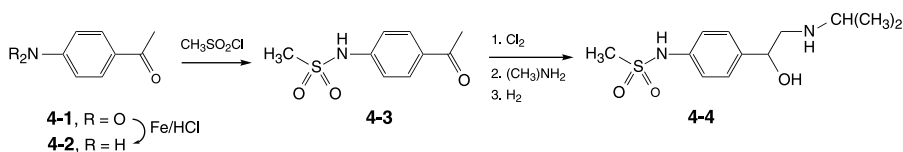
The history of drug discovery aptly illustrates the important role played in this process by serendipity. Clinical investigations on **sotalol** revealed that the agent had pronounced activity as an antiarrhythmic agent, an action that could be, and was, logically attributed to the compound's β-blocking action. The observation that both enantiomers seemed to have equal potency, however, cast some doubt on this explanation for the antiarrhythmic activity. Subsequent work, perhaps spurred by this discrepancy, had in fact shown that sulfonanilides, which lack the

phenethanolamine side chain, show quite good antiarrhythmic activity in their own right. This observation has led to a series of antiarrhythmic agents whose structures have in common only a sulfonamide group. The first of these agents, **ibutilide** (**5-3**), incorporates a vestige of the ethanolamine side chain, in the form of a 1,4-aminoalcohol. Preparation starts with the Friedel–Crafts acylation of methanesulfonylanilide with succinic anhydride to give the keto-acid (**5-1**). Reaction of the corresponding acid chloride with *N*-ethyl-*N*-heptylamine gives the amide (**5-2**). Reaction with lithium aluminum hydride in the cold serves to reduce both the amide and ketone to afford **ibutilide** [3]. Further work shows that activity is retained when the hydroxyl group is replaced by polar groups such as an amide or even a non-enolizable sulfonamide. Ester interchange of the mesylate from ethyl *para*-aminobezoate with *N,N*-diethyl-ethylenediamine gives the antiarrhythmic agent **sematilide** [4] (**5-5**). In a similar vein, reaction of sulfonyl chloride (**5-6**) (from reaction of methanesulfonylanilide and chlorosulfonic acid), with *N,N'*-di-*iso*-propylethylenediamine gives **risotilide** (**5-7**) [5].
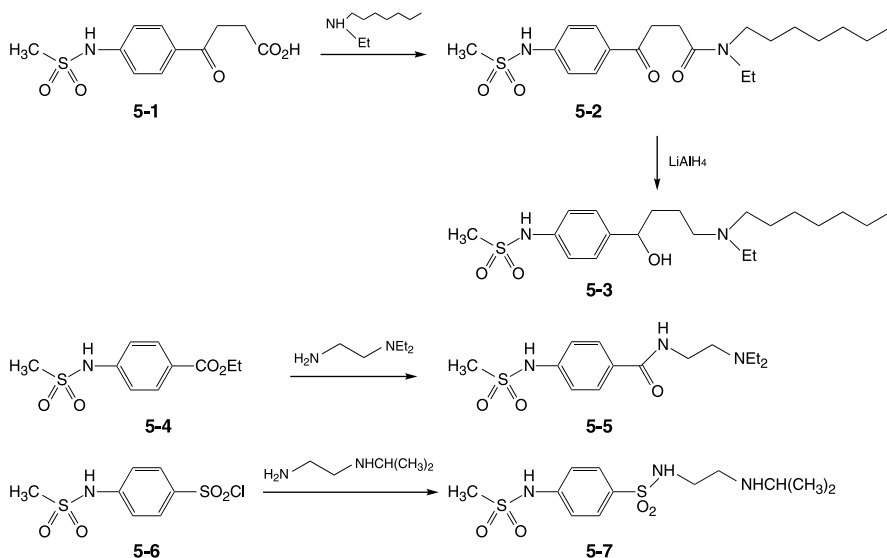

A more recent example, which involves an enantiomerically pure compound, reverts to the original lead by incorporating a hydroxyl group on the benzylic carbon. Preparation of this close relative of ibutilide (**5-3**) uses the same starting material. Acylation of *n*-dibutylamine with the acid chloride from the treatment of (**6-1**) with *tert*-butylcarbonyloxy chloride leads to the amide (**6-2**). Reduction of the carbonyl group in this compound with chloro-(+)-diisopropylcamphemyl borane (DIPCl) proceeds to afford the *R* alcohol (**6-3**) in high enantiomeric excess.

Reduction of the amide function with lithium aluminum hydride then reduces the amide carbonyl to afford **atilide** (**6-4**) [6].
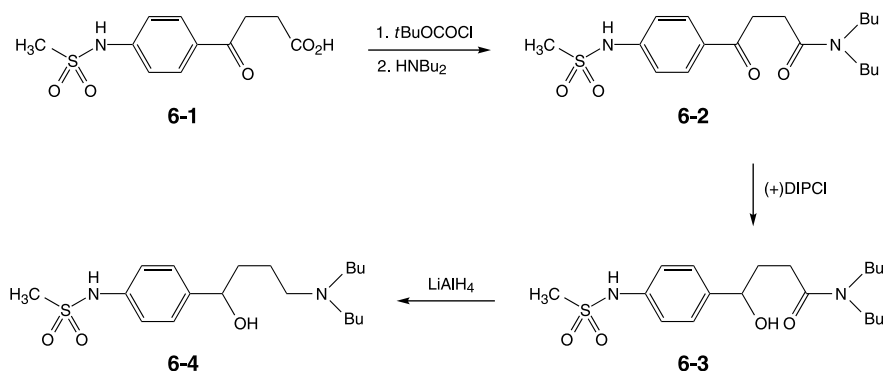

Antiarrhythmic activity is interestingly maintained in a compound whose structure does not bear the slightest resemblance to adrenergic agents. Alkyation of *N*-methyl-4-nitrophenethylamine (**7-2**) with chloroethyl ether (**7-1**) leads to the tertiary amine (**7-3**). The nitro group is reduced by any of several methods to afford aniline (**7-4**). Acylation of the newly formed amino group with methanesulfonyl chloiide affords the antiarrhythmic agent **dofetilide** (**7-5**) [7].
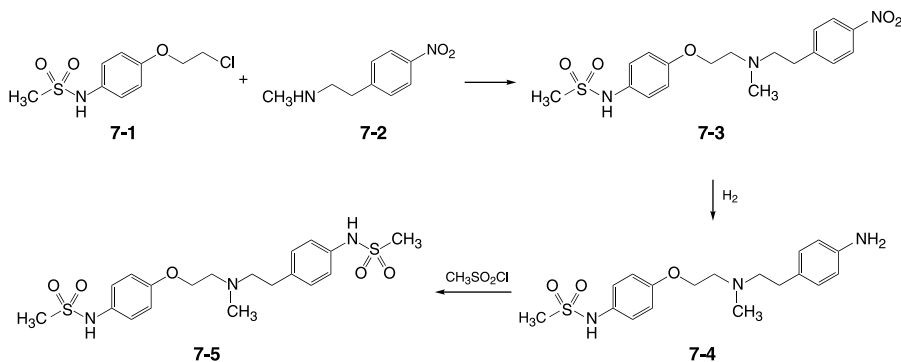
The β-adrenergic system is itself further divided into several branches; receptors for these subsystems show different ligand structural preferences. The cardio-vascular system is responsive largely to β$_1$-adrenergic agents; activation leads to increases in blood pressure and heart rate. Bronchioles constitute an important target for β$_2$-adrenergic agonists; activation leads to relaxation and resolution of bronchospasms. Use of the classical β agonist **isoproterenol** (**2-3**) for the treatment of asthma is limited by the side effect due to poor selectivity for β$_2$ receptors.

Compounds that exhibit preferential β_2-adrenergic agonist activity have proven to be very useful in the treatment of asthma. The compounds discussed below represent only a very small selection from the dozens of antiasthma compounds that have been investigated in the clinic. It is of interest to note that while the replacement of the *para* hydroxyl of a phenylethanolamine by sulfonanilido as in **sotalol** (**2-4**) leads to an antagonist, the corresponding change at the *meta* position in this series leads to an adrenergic agonist that shows selectivity for β_2 receptors. The synthesis of this agent, **soterenol** (**8-6**), starts with the nitration of *p*-benzyloxyacetophenone. Reduction of the intermediate nitro compound (**8-2**) with hydrazine in the presence of Raney nickel gives the corresponding aniline (**8-3**). This is then converted to the sulfonamide (**8-4**), by reaction with methane-sulfonyl chloride. Bromination of the methyl group of the ketone followed by displacement with isopropylamine leads to the intermediate (**8-5**). Reduction of the ketone to an alcohol followed by hydrogenolysis of the benzyl protecting group affords **soterenol** (**8-6**) [8].
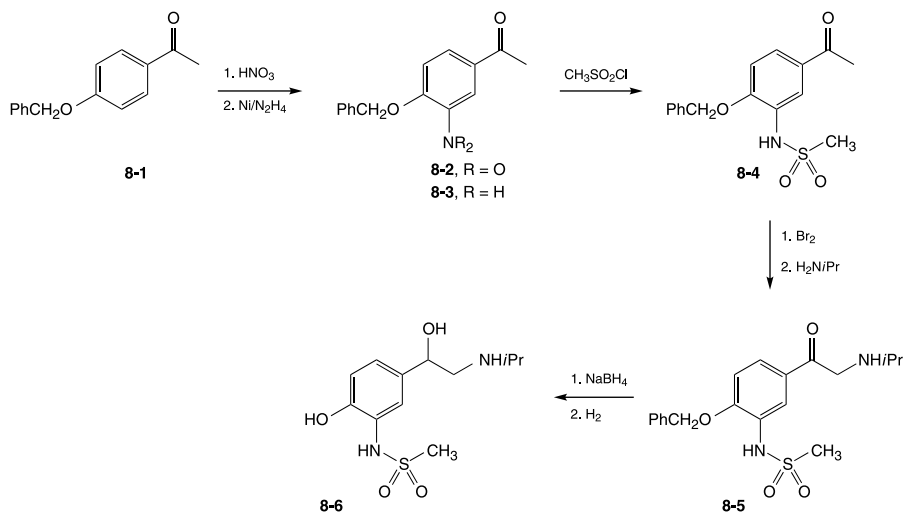

A simple aliphatic alcohol at the *meta* position is actually sufficient for conferring β_2 agonist activity to a phenolethanolamine as demonstrated by the very widely used drug **albuterol** (**9-4**), formerly known as **salbutamol**. The product (**9-1**) from the acetylation of methyl salicylate provides the starting material. The usual amination sequence using *tertiary*-butylbenzylamine gives the corresponding aminoketone (**9-2**). Reduction by means of lithium aluminum hydride converts the ester to a carbinol and the ketone to the requisite alcohol in a single step. The benzyl protecting group is then removed by catalytic reduction to afford **albuterol** (**9-4**) [9].
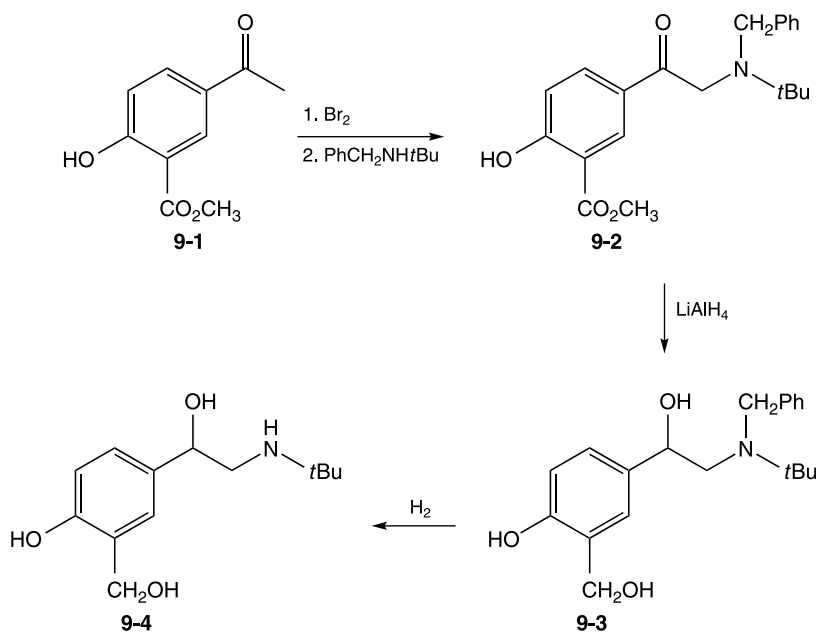
The analogue (**10-5**) of albuterol in which the amino group is primary (**10-1**) pro-vides the starting material for a significantly more lipophilic β agonist. Construction of the side chain for this compound involves mono-alkylation of 1,6-dibromohexane (**10-4**) with 2-phenylethanol to give bromide (**10-2**). Alkylation of (**10-1**) with that halide gives **salmeterol** (**10-5**) in a single step [10].
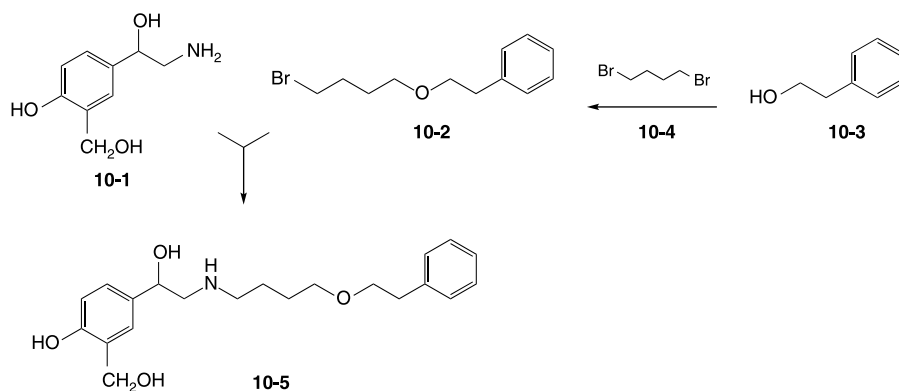
A selective β_2 agonist is retained when the phenol at the *meta* position is replaced by a urea group. Sequential reactions of the **soterenol** intermediate (**11-1**) with phosgene and then ammonia lead to urea (**11-2**). The by-now familiar bromination–amination sequence gives the aminoketone (**11-3**). The ketone is then reduced to an alcohol with a sodium borohydride and the benzyl protecting group is removed by hydrogenolysis to give **carbuterol** (**11-4**) [11].
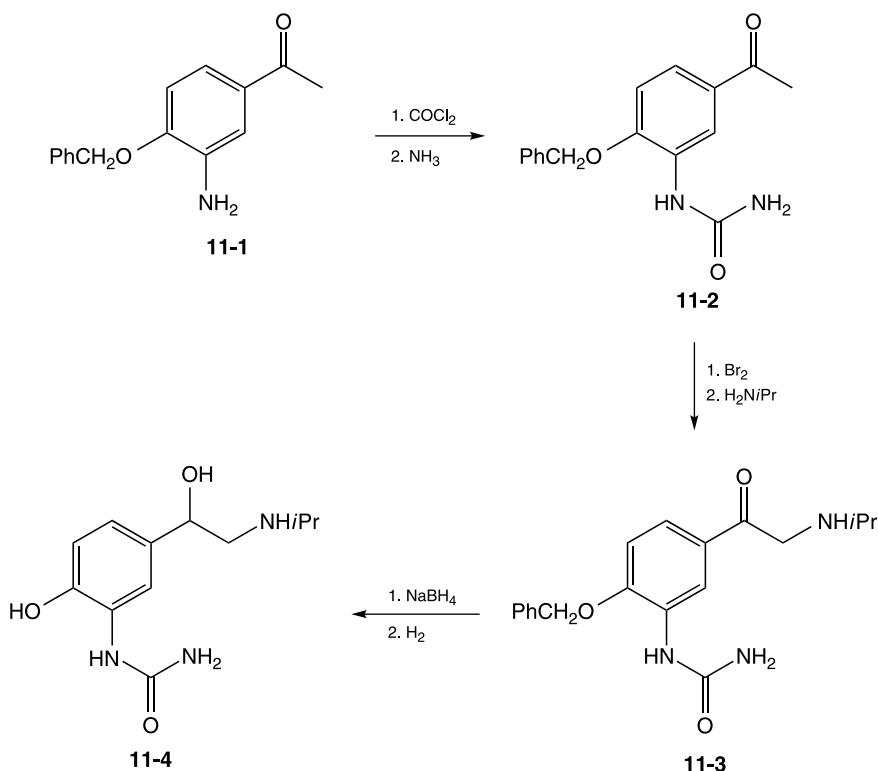
The activity of β-blockers as antihypertensive agents is discussed in greater detail in the section that follows; it is, however, relevant for the discussion at hand to note that some of the shortcomings of those drugs can to some extent be overcome by incorporating a degree of α-adrenergic blocking activity into the compound. The prototype-combined α/β-blocker, **labetolol** (**12-6**), incorporates an amide group on the phenylethanolamine moiety reminiscent of the urea on **carbuterol**. Friedel–Crafts acetylation of salicilamide (**12-1**) gives substituted acetophenone (**12-2**); this is then converted to bromoketone (**12-3**). Use of that intermediate to alkylate 4-phenylbultyl-2-amine (**12-4**) gives the aminoketone (**12-5**). The ketone is then reduced to an alcohol by catalytic hydrogenation [12]. The resulting compound, **labetolol** (**12-6**), consists of a mixture of two diastereomers as a consequence of the presence of two chiral centers.
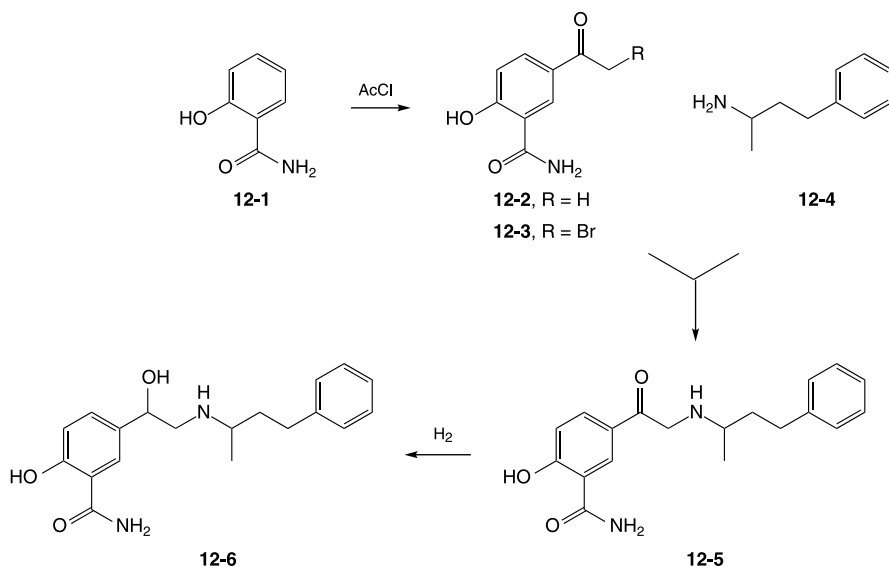
The discovery of a third subset of adrenergic binding sites, the β_3-receptors, has led to a compound that provides an alternate method to currently available anticholinergic agents for treating overactive bladders. There is some evidence, too, that β_3 agonists may have some utility in treating Type II diabetes. Synthesis of the compound begins with the construction of the biphenyl moiety. Thus, condensation of methyl *meta*-bromobenzoate (**13-1**) with *meta*-nitrophenylboronic acid (**13-2**) in the presence of palladium tetrakistriphenylphosphine leads to the coupling product (**13-3**). The nitro group is then reduced to the corresponding amine (**13-4**). Alkylation of this with the *t*-BOC protected 2-bromoethylamine (**13-5**) leads to the intermediate (**13-6**). Treatment with acid removes the protecting group to give the primary amine (**13-7**). Condensation of this last product with *meta*-chlorostyrene oxide leads to the formation of **solabegron** (**13-9**), a molecule that incorporates the aryl ethanolamine moiety present in the great majority of compounds that act on adrenergic receptors [13].
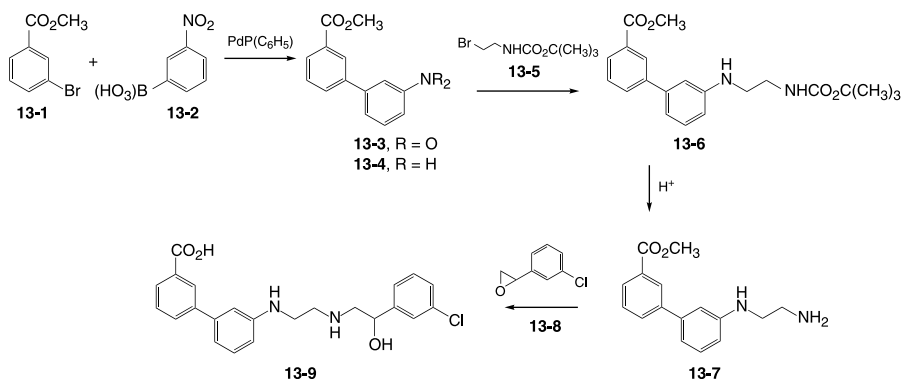
An agent that acts on a subset of adrenergic α-receptors, specifically alpha-1A/1L receptors, has also shown activity on the same clinical endpoint. The synthesis starts with Mitsonobu alkylation of the nitrophenol (**14-1**) h *N*-trityl protected imidazole methylcarbinol (**14-2**) to give the ether (**14-3**). The nitro group on the benzene ring is then reduced to the primary amine by any of several methods (**14-4**). The resulting aniline is then converted to the corresponding sulfonamide (**14-5**) reaction with methanesulfonyl chloride. Hydrolysis with mild acid then removes the trityl protecting group to afford **dabuzalgron** (**14-6**) [14].
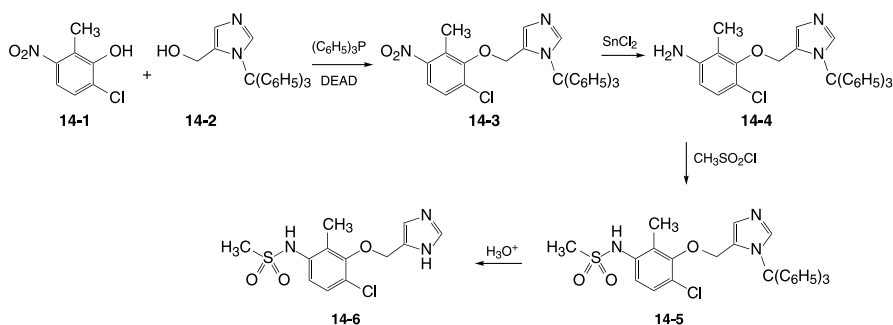
Chloramphenicol (**15-6**), which can formally be classified as a phenylethanolamine derivative, exhibits far different activity from the other compounds endowed with that structural feature. This compound actually comprised one of the first orally active antibacterial agents. The one-time extensive use of this drug declined with the recognition of its propensity to cause blood discrasias and the availability of safer alternatives. The compound is, however, still in wide use as a topical antibacterial agent. The relatively simple structure of this product from *Streptomyces venezuela* fermentation, initially known as **chloromycetin**, led early on to its production by total synthesis. The comparatively short and straightforward route presented in the first synthesis does, however, suffer from a lack of steric control. The first step in the synthesis consists of aldol condensation of benzaldehyde with 2-nitroethanol to give a mixture of all four enantiomers of nitropropanediol (**15-1**); the total mixture is reduced catalytically to the corresponding mixture of aminodiols (**15-2**). The *threo* isomer is then separated by crystallization and resolved as a diasteromeric salt to give the D(−) isomer. Acylation with dichloroacetyl chloride initially gives the triacetate, and saponification gives the desired product (**15-3**). The free hydroxyls are then converted to the acetates by means of acetic anhydride and the resulting product (**15-4**) nitrated with the traditional nitric–sulfuric acid mixture (**15-5**). Saponification then removes the acetate protecting groups and affords **chloramphenicol** (**15-6**).
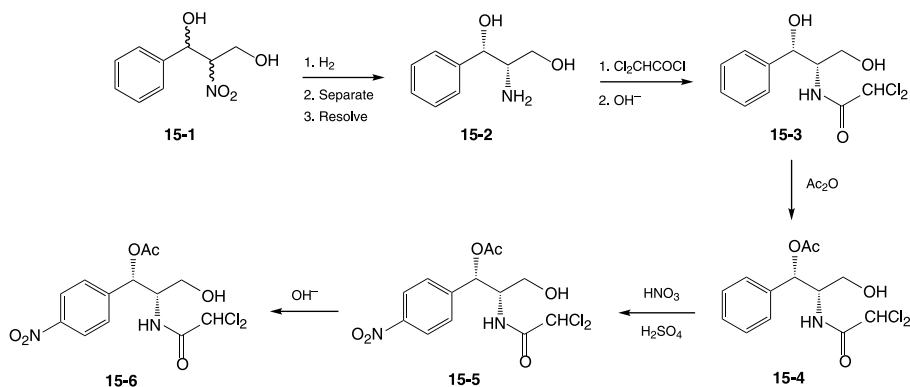
The upsurge of interest in enantioselective synthesis combined with the availability of new methods and reagents for achieving such transformations led to a re-examination of the syntheses for many drugs that are formulated as pure enantiomers. One novel approach to a **chloramphenicol** intermediate starts with the oxidation of cinnamyl alcohol (**16-1**) with Sharpless reagent (*tertiary*-butyl hydroperoxide, titanium isopropoxide, L($+$)diisopropyl tartrate) to give enantiomerically pure epoxide (**16-2**). Ring opening of the epoxide with benzoic acid in the presence of titanium isopropoxide gives the diol benzoate with an inverted configuration at the central side chain alcohol; carefully controlled benzoylation leads to (**16-3**), in which the second alcohol remains free. This is then converted to a methanesulfonate (**16-4**), and that group is displaced by azide to afford azide 79; the last reaction proceeds with an inversion of configuration to give the desired stereochemistry. Catalytic reduction of the azido group to a primary amine gives the entantiomerically pure intermediate (**16-6**); simple saponification would then afford the intermediate (**15-2**) in the original scheme as a pure enantiomer [15].
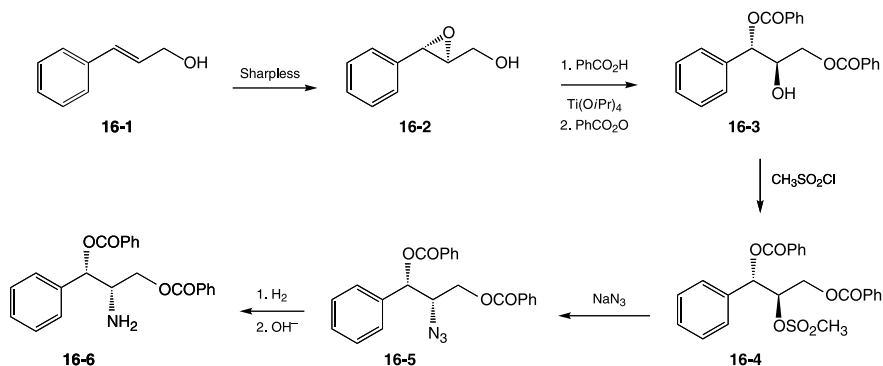
2.2. ARYLOXYPROPANOLAMINES

2.2.1. β-Blockers

The discovery that β-sympathetic blocking agents, for example **sotalol**, seemed to have useful clinical activity in treating the symptoms of cardiovascular disease such as angina and arrhythmias engendered considerable interest in this class of agents. The finding that β-blocking activity was retained when an oxymethylene ($-OCH_2-$) group was interposed between the aryl group and the ethanolamine side chain made access to this class of compounds much easier. One of the first drugs of this new structural class, **propranolol** (**17-1**), found extensive clinical use in the treatment of angina and arrhythmias. This led to the unexpected finding that the drug caused a decrease in blood pressure among those patients whose disease was complicated by hypertension. The usefulness of the drug in treating heart disease was not unexpectedly attributed to a decrease in the stimulation of cardiac β-receptors by endogenous epinephrine. This activity would, however, be expected to increase blood pressure by blocking the largely relaxant effect of that neurotransmitter on the vasculature. This seemingly paradoxical action of β-blockers is now attributed to a decrease in the force of cardiac contraction caused by these drugs. This serendipitous finding opened an enormous market for β-blockers as antihypertensive drugs with a consequent increase in research on this class of drugs. The paragraphs below cover only a fraction of the enormous number of aryloxypropanolamines that have been reported, or, for that matter, the very large number of drugs on the market. The early β-blockers, such a **propranolol**, showed some tendency to exacerbate bronchoconstriction in patients who also had asthma, an effect attributed to the blockade of the relaxant effect of epinephrine on bronchioles. The finding that the vasculature is populated by β_1-receptors while those in the lungs consist mainly of β_2-receptors has led to an emphasis on so-called β_1-selective drugs for controlling blood pressure.
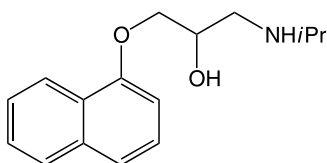

17-1

The key, and usually final, sequence in the synthesis of β-blockers consists of the addition of the propanolamine side chain. The customary approach consists of an initial alkylation of the appropriate phenoxide with epichlorohydrin (ECH in schemes below). As one of the two possible reaction pathways, the phenoxide initially attacks the oxirane; the resulting alkoxide from the opening of the epoxide

will then displace the adjacent chlorine to form a new epoxide ring. Alternatively, the phenoxide may simply displace halogen directly in an SN_2; both pathways lead to the same glycidic ether. It is of note that the central asymmetric carbon retains its configuration in both schemes, an important consideration when using chiral epichlorohydrin or an equivalent intermediate for the synthesis of enantiomerically defined drugs. The opening of the epoxide ring in the glycidic ether with an appropriate amine, most often isopropylamine or *tertiary*-butylamine, leads to the aryloxypropanolamine compound. These reagents invariably consist of primary amines, as it is generally recognized that only compounds in which nitrogen is secondary block β-adrenergic receptors.

Aryloxypropanolamine Construction
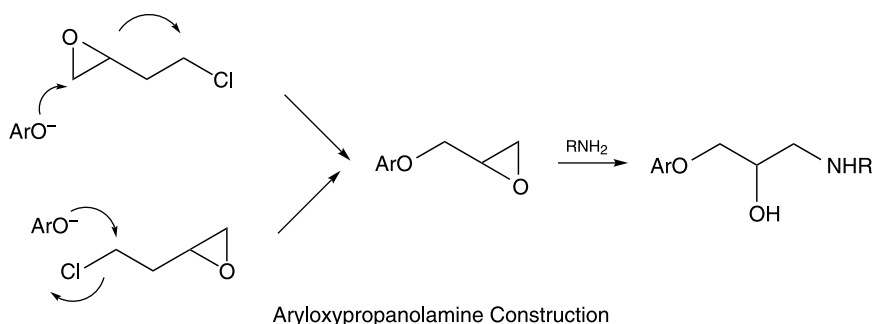
The synthesis of a typical β-blocker starts with the mono-alkylation of catechol to give the ether (**19-1**). Application of the standard side chain building sequence leads to the nonselective β-blocker **oxprenolol** (**19-2**) [16] (the olol ending is approved USAN nomenclature for β-blockers). **Atenolol** (**19-5**) is one of the most widely used $β_1$ selective agents. The requisite phenol (**19-4**) can be obtained by ester interchange of methyl 4-hydroxyphenylacetate (**19-3**) with ammonia. Elaboration of the thus obtained intermediate (**19-4**) via the customary scheme then affords **atenolol** (**19-5**) [17].

Injectable β-blockers have found an important use in the treatment of cardiac infarcts as a means of reducing demands on the injured heart muscle. This strategy carries with it, however, the hazard that excessive blood levels of drug cannot be quickly withdrawn in those cases where heart failure sets in. An injectable β-blocker with a very short half-life in the circulation was designed to address this problem; the terminal ester group in this compound, **esmolol** (**19-7**), is very quickly hydrolyzed to the carboxylic acid by serum esterases. The metabolite acid lacks β-blocking activity and is quickly cleared from the circulation. The drug is prepared by subjecting methyl 4-hydroxyhydrocinamate (**19-6**) acid to the usual side chain forming sequence [18].
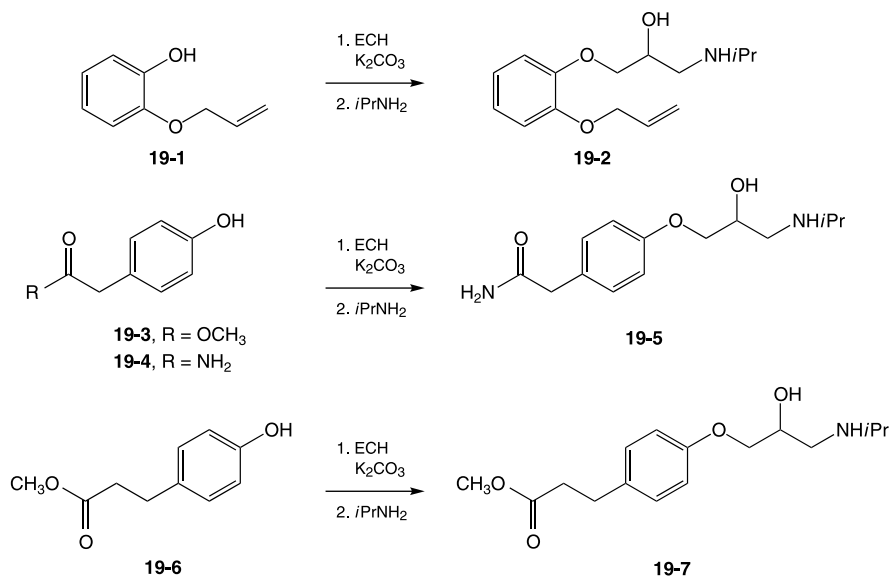
Interposition of the oxymethylene moiety is not by itself a sufficient condition for changing an ethanolamine from agonist to antagonist. The analogue of epinephrine lacking the *meta* hydroxyl group is known to be a reasonable potent adrenergic agonist. The local vasoconstricting activity of this compound, **synephrine**, accounts for its use in nasal decongestants. Interposition of the oxymethylene in
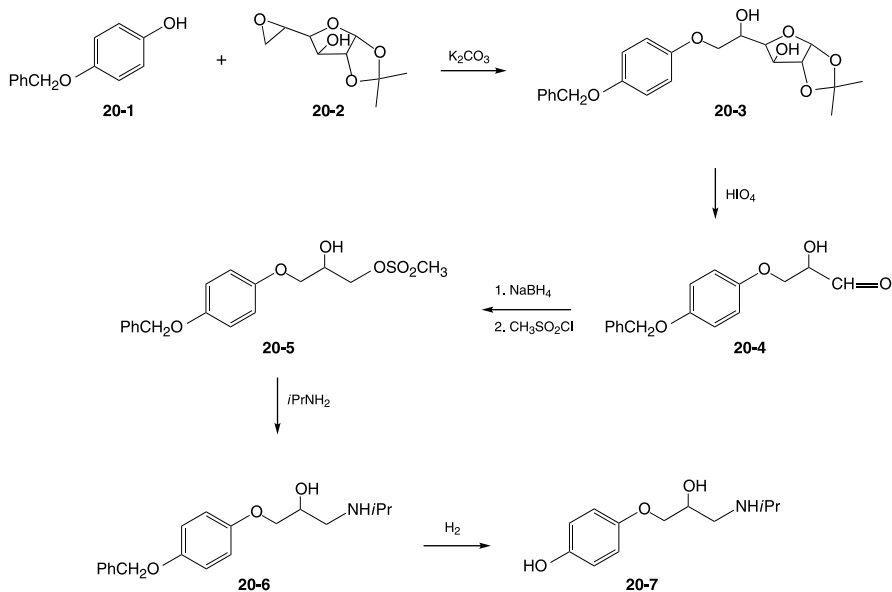
that compound (and the replacement of *N*-methyl by isopropyl) leads to **prenalterol** (**20-7**), a β-sympathetic agonist that shows selectivity for β$_2$-receptors. The enantio-selective synthesis of this compound incorporates the required chiral carbon in the first step of the synthesis by using a carbohydrate-derived intermediate. Note that the central carbon on the epoxide is the sole chiral carbon retained in the final product. A more modern synthesis of this compound would probably depend on glycidic ether formation with currently commercially available chiral epichlorohydrin. Monoalkylation may reside, in this case, in the opening of the epoxide (**20-2**) obtained in several steps from D-glucofuranose, with the monobenzyl ether (**20-1**) from hydro-quinone, leads to the intermediate (**20-3**). Scission of one of the 1,2-glycol linkages in the carbohydrate moiety with periodate gives the hydroxyaldehyde (**20-4**), a compound now relatively inert to the reagent. Reduction with sodium borohydride followed by methanesulfonyl chloride gives the mesylate (**20-5**) from acylation at the more reactive primary alcohol. Displacement of this leaving group by isopropylamine completes the construction of the aminoalcohol (**20-6**). Hydrogenation over palladium on charcoal removes the benzyl protecting group to afford, finally, **prenalterol** (**20-7**) [19].

2.2.2. Non-Tricyclic Antidepressants (SSRIs)

The development of the tricyclic antidepressant drugs in the late 1950s followed hard on the heels of the discovery of the structurally closely related antipsychotic agents; a discussion of the chemistry of those drug classes will be found in Chapter 3. Very widespread use of the former, not unexpectedly, uncovered a series of side effects. The most troubling of these involved occasional findings of cardiotoxicity; the fact that this occurred with compounds with varying structures suggested that this could be a consequence of the agent's mode of action. The subsequent development of very active open chain antidepressant compounds made available drugs devoid of that limitation as they act by a quite different mechanism. It has been determined that this class of compounds interacts with presynaptic receptors in the brain so as to inhibit the re-uptake of neurotransmitters (serotonin or norepinephrine) from the synaptic cleft. The majority of non-tricyclic antidepressants are selective for serotonin and are often grouped under the acronym SSRI (selective serotonin reuptake inhibitors).The side effects, true and/or imagined, of the first of these compounds to be marketed **fluoxetine** (**21-7**) have been widely publicized under its more familiar soubriquet, Prozac®. The first published synthesis of this compound starts with the Mannich base (**21-1**) from the reaction of acetophenone, formaldehyde, and dimethyl-amine. The ketone is then reduced to an alcohol (**21-2**), and that is converted to chloride (**21-3**) by any of several methods such as reaction with hydrogen chloride in chloroform. The displacement of halogen with the phenoxide from treatment of *para*-trifluoromethylphenol (**21-4**) leads to the corresponding *O*-alkyl ether. One of the methyl groups on nitrogen is then removed by treatment of the intermediate with cyanogen bromide followed by hydrolysis (von Braun reaction) or with the recently developed modification that uses ethyl chloroformate. The same sequence using the monomethyl ether of catechol (**21-5**) leads to **nisoxetine** (**21-8**) [20]. One of the

two enantiomers of SSRIs is a good deal more potent than its counterpart, as would be expected from agents that bind to inherently chiral receptors. The current trend to formulate drugs that consist solely of the active isomers is reflected in the fact that the analogue, **tomexetine** (**21-9**), consists of the pure levorotatory isomer. In this case the product from the standard sequence starting with *ortho*-cresol methyl ether (**21-6**) is resolved by salt formation with D-(+) mandelic acid [21].
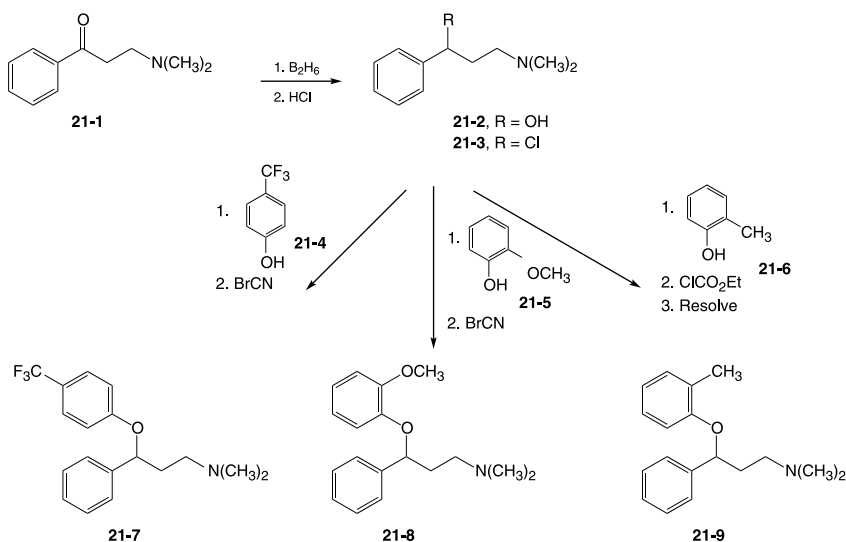

A recent stereoselective synthesis for one of these drugs, **reboxetine** (**22-9**), starts with the commercially available chiral (*S*)-3-aminopropanediol (**22-1**). Acylation with chloroacetyl chloride leads to the amide (**22-2**). Treatment of that intermediate with a strong base results in the internal displacement of halogen with the consequent formation of the morpholine ring (**22-3**). Reduction of the amide function with the hydride Red-Al (sodium *bis*(methoxyethoxy)aluminum hydride) forms the desired morpholine (**22-4**). The secondary amino group is protected as its BOC derivative (**22-5**) by acylation with *tert*-butoxycarbonyl chloride. The next step involves the oxidation of the primary alcohol with the unusual reagent combination consisting of 2,2,6,6-tetramethylpiperidinyl-*N*-oxide (TEMPO) and trichloroisocyanuryl chloride. There is thus obtained aldehyde (**22-6**). Condensation of this intermediate with diphenyl zinc obtained by treating phenylmagnesium bromide with zinc bromide affords the secondary carbinol (**22-7**). The same reaction in the absence of zinc leads to the recovery of unreacted aldehyde. The desired diastereomer is formed in an ~3 : 1 ratio with its isomer. The final piece could be added by conventional means such as, for example, reaction with 2 ethoxyphenol in the presence of DEAD and carbon tetrachloride. Reaction of (**22-7**) with the chromyl reagent (**22-8**) followed by oxidative removal of chromium by iodine gives the coupling product in high yield. Removal of the BOC protecting group with trifluoroacetic acid completes the synthesis of (*S,S*)**reboxetine** (**22-9**) [22].
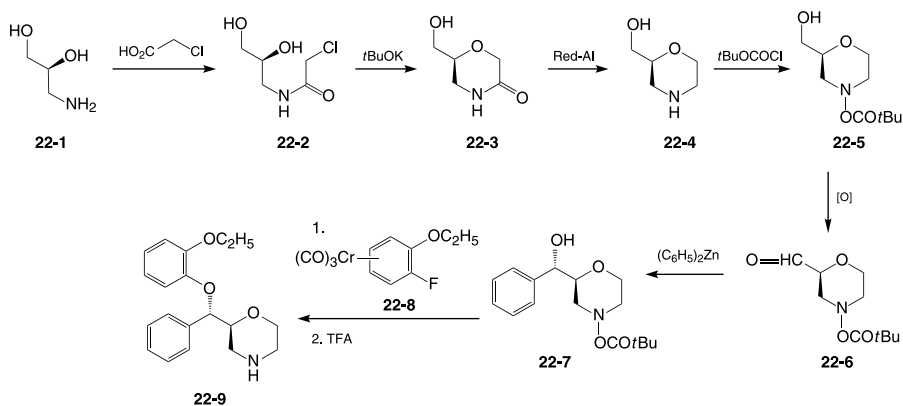
The nature of the aromatic substituents is apparently not critical for SSRI activity, as indicated by the structure of **duloxetine** (**23-5**), where one ring is replaced by thiophene and the other by naphthalene. The synthesis starts as above by the formation of the Mannich base (**23-1**) from 1-acetylthiophene with formaldehyde and dimethylamine. Treatment of that intermediate with the complex from lithium aluminum hydride and the 2*R*,3*S* entantiomer of dimethylamino-1,2-diphenyl-3-methylbutane-2-ol gives the *S* isomer (**23-2**) in high enantiomeric excess. Treatment of the alkoxide from (**23-2**) and sodium hydride with 1-fluoronaphthalene leads to the displacement of halogen and thus the formation of ether (**23-2**). The surplus methyl group is then removed by yet another variant of the von Braun reaction that avoids the use of a base for saponifying the intermediate urethane. Thus, reaction of (**23-3**) with trichloroethyl formate leads to the *N*-demethylated chlorinated urethane (**23-4**). Treatment of that intermediate with zinc leads to a loss of the carbamate and the formation of the free secondary amine **duloxetine** (**23-5**) [23].
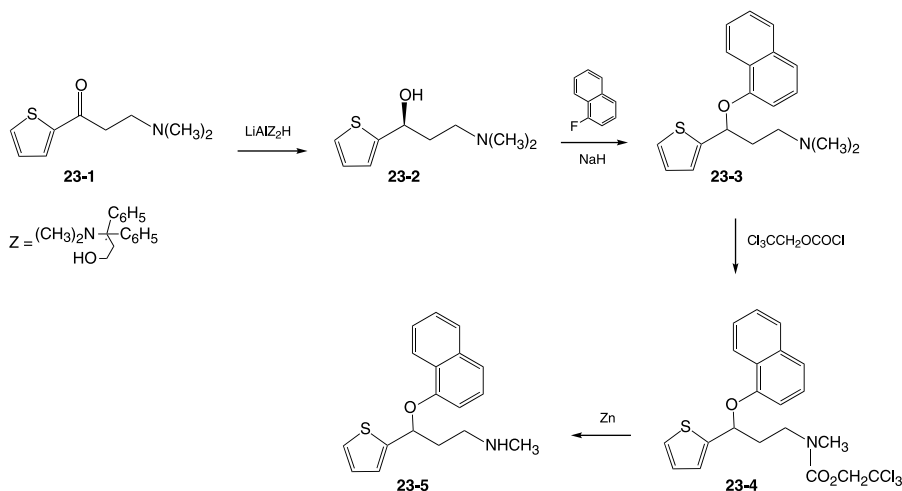
N-demethylation is a well-recognized drug metabolism transform that more often than not leads to the inactivation of drugs. It is consequently of interest that this hypothetical **fluoxetine** metabolite shows the same activity as the parent. The synthesis of this agent, as in the preceding example, reverses the ether formation step. Thus, displacement of fluorine from 4-fluorotrifluoromethylbenzene (**24-2**) in an aromatic nucleophilic replacement reaction with the alkoxide from (**24-1**) (Phth = phthaloyl) affords the ether (**24-3**). Removal of the phthaloyl protecting group by reaction with hydrazine gives the antidepressant **seproxetine** (**24-4**) [24].
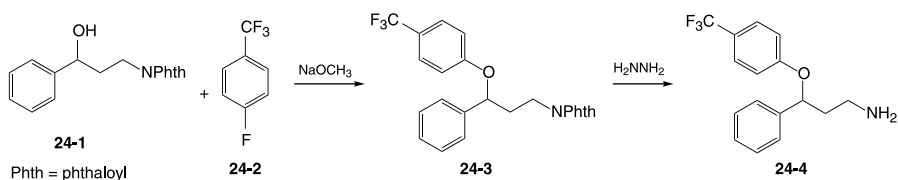
SSRI activity is interestingly maintained even in the absence of one of the aromatic rings. Attaching the oxygen atom to an oxime leads to the antidepressant **fluvoxamine**. The requisite oxime (**25-2**) is obtained by reaction of the starting ketone (**25-1**) with hydroxylamine. Treatment of that intermediate with ethylene oxide adds the ether-linked side chain that will carry the amine. The hydroxyethyl product (**25-3**) is thus converted to its mesylate by means of methanesulfonyl chloride. This leaving group is then displaced by any one of several methods to afford the primary amine and thus **fluvoxamine** (**25-4**) [25].
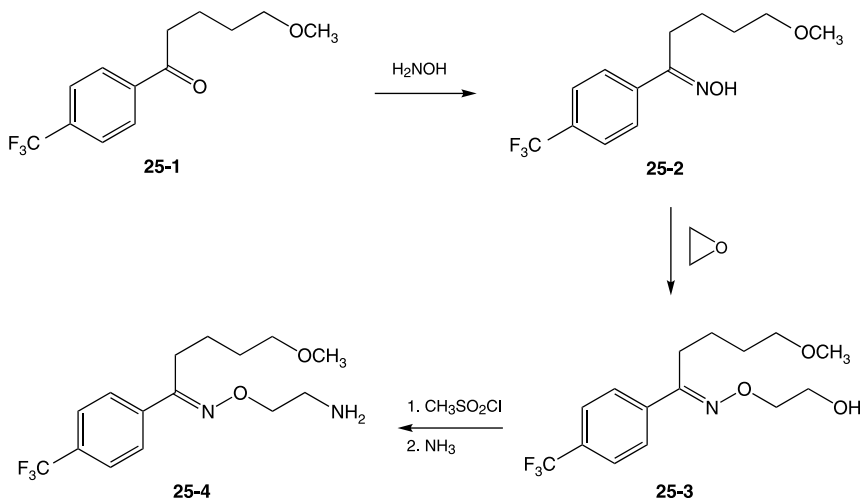
2.3. ARYLSULFONIC ACID DERIVATIVES

2.3.1. Antibacterial Sulfonamides

The quantum leap in human life expectancy observed since the beginning of the twentieth century is most commonly attributed by epidemiologists to the decreased mortality and morbidity from infectious disease. The largest single factors leading to this decrease are improvements in sanitation and the availability of antibacterial drugs. The first of the many available synthetic antibacterial agents available today was in fact discovered due to a set of adventitious events. Intrigued by the observation that certain organic dyes showed strong affinity for specific bacteria, Domagk and his collaborator Klarer in the early 1930s in Germany initiated a synthesis and screening program to test the antibacterial action of such dyes. It was to prove crucial that all compounds were tested *in vivo* in mice, rather than *in vitro*, as was then, and is now again, far more customary. The dramatic curative action of a red dye dubbed **prontosil** in infected mice attracted immediate attention. The dye became available for clinical use when the activity was found to hold up in humans as well. Puzzled by the observation that **prontosil** failed to show activity in any of the then-current *in vitro* antibacterial assays, Bovet and colleagues in France considered the possibility that the activity was in fact due to a metabolite. Work based on that premise demonstrated that one of the metabolites from the cleavage of the $N-N$ azo link, **sulfanilamide**, accounted for all the activity of **prontosil** both *in vivo* and *in vitro*; the other metabolite, 1,2,4-triaminobenzene, was devoid of activity by either route. **Sulfanilamide** quickly replaced the dye as the drug of choice and gained widespread use just in time to save innumerable lives of wound victims in World War II.
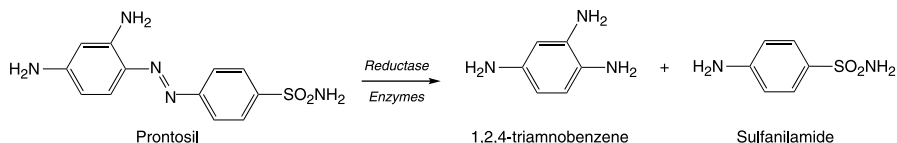
Elucidation of the mechanism of action of the sulfonamides served to clarify both their activity and marked selectivity for bacteria. Mammals are unable to synthesize the folates involved in nucleotide synthesis and depend on obtaining those crucial compounds from their diet. In contratst to this, bacteria must synthesize those compounds *de novo*. *Para*-aminobenzoic acid (PABA) comprises an important structural unit of folates. It has been rigorously demonstrated that sulfonamides act as competitive inhibitors for the bacterial enzyme that incorporates PABA, dihydropteroate synthetase; the enzyme presumably recognizes the acidic sulfonamide proton as a carboxylate hydrogen. Incorporation of the misconstrued sulfa drugs brings folate synthesis to a halt. The rather strict structural requirements in this class of antibacterial agents directly reflect the mode of action: The presence of a primary aniline group and at least one sulfonamide proton are mandatory for activity; additional substituents on the ring decrease activity by interfering with recognition.

The synthesis of the parent compound, **sulfanilamide** (**27-1**), is a straightforward exercise in aromatic chemistry. (It is of interest to note that the preparation of this drug starting from benzene was at one time a standard assignment in beginning undergraduate organic chemistry labs; this exercise probably set more than one medicinal chemist, including the author, on his or her career path.) The key reaction involves the chlorosulfonation of acetanilide to give sulfonyl chloride (**27-2**). Reaction with ammonia followed by acid catalyzed hydrolysis of the acetamide amide gives **sulfanilamide** itself. This same general reaction with other amines or heterocyclic amines leads to a host of other drugs (**27-3**) that have virtually the same antibacterial spectrum but may differ in their pharmacokinetic properties. The 13th edition (2001) of the *Merck Index*, for example, lists over 50 different compounds under the category for sulfonamide antibiotics.
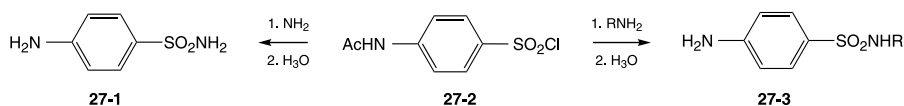
A sulfonamide that seemingly violates the requirement of a primary amine at the 4 position, **sulfasalazine** (**28-5**), has proven useful for the treatment of ulcerative colitis, a poorly understood and often fatal disease of the colon. This compound undergoes the same metabolic cleavage by bacteria in the gut as does prontosil, that is, cleavage of the azo linkage. There is good evidence in this case, however, that the active moiety is in fact the 4-aminosalicylic acid (**28-6**) metabolic product rather than the sulfonamide. **Sulfasalazine** is thus apparently a prodrug for delivering that compound directly to the disease site. The starting material for that agent, **sulfapyridine** (**28-2**), is prepared by reaction of 2-aminopyridine with sulfonyl chloride (**27-1**). The aniline function is then converted to a diazonium salt by reaction with nitrous acid. Coupling of the salt with salicylic acid proceeds at the 4 position to give **sulfasalazine** (**28-5**) [25]. **Olsalazine** (**28-7**), designed after the mode of action of the parent agent had been clarified, represents a more direct approach for delivering the active moiety to the lower intestine, with both halves of the molecule providing 4-aminosalicylic acid on the reductive cleavage of the azo linkage. The compound is prepared by coupling the diazonium salt from methyl 4-aminosalicylate (**28-6**) with methyl salicylate, followed by hydrolysis of the esters [26].
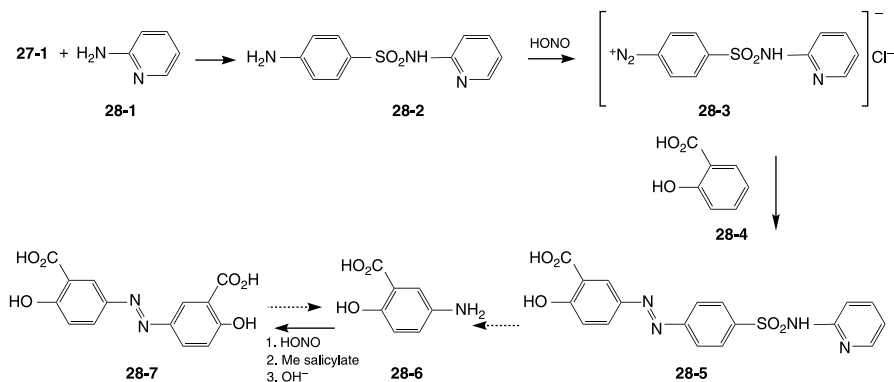
2.3.2. Diuretic Agents

Widespread use of the sulfonamide antibacterial agents uncovered a series of minor side effects. Among these was an increase in urine output when the drugs were administered at high doses. This adventitious observation was the spur for work in modifying the molecule so as to optimize what had been a side effect since the only diuretic drugs available at that time were several organomercurials whose use was limited due to the well-known toxicity of mercury and its derivatives. One of the first successes lay in the finding that compounds in which a second sulfonamide group was added at the *meta* position showed reasonable diuretic activity. These compounds are devoid of antibacterial activity since they now show not the slightest resemblance to *para*-aminobenzoic acid.

Treatment of chlorobenzene with chlorosulfonic acid under forcing conditions leads to the *meta* disubstituted sulfonyl chloride (**29-1**); ammonolysis of that intermediate leads to the diuretic agent **chlorphenamide** (**29-2**) [27]. In a similar vein, *ortho*-chlorophenol (**29-3**) yields *bis*-sulfonamide (**29-4**) on sequential reaction with chlorosulfonic acid and ammonia. Hydroxyl groups in heterocyclic compounds behave very much like enol forms of carbonyl groups; they can thus be replaced by chlorine. The same seems to apply to electron-deficient benzene rings. The presence of the two strongly electron withdrawing sulfonamides *meta* to the hydroxyl in (**29-4**) seems to make that assume the enol character as well. Reaction of that intermediate with phosphorus trichloride thus leads to the formation of the dichloro compound; there is thus obtained **dichlorphenamide** (**29-5**) [28]. It should be noted that the simple *bis*-sulfonamide diuretics have been largely displaced by heterocyclic thiazides (Chapter 11) and the so-called high ceiling agents.
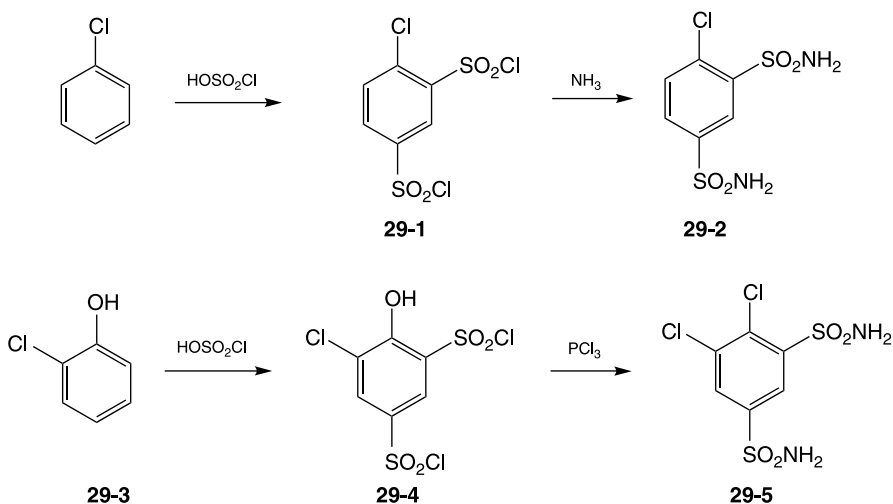
Though the terms "potency" and "activity" are often used interchangeably, albeit erroneously, in the literature they in fact denote different aspects of a given compound's biological action. The dose of a given agent required to produce a stated effect, such as, for example, 25% inhibition of an enzyme, is correctly termed as its potency; the maximal effect, in the same case the highest percent inhibition

achievable with the same agent, is its activity. The simple disulfonamides as well as the thiazide diuretics are often termed "low ceiling" compounds because increasing doses will not lead to increased diuresis above a threshold level. The "high ceiling" compounds cause dose-related increases in diuresis beyond those achievable with their low ceiling counterparts. The two high ceiling diuretics, **furosemide (30-4)** and **azosemide (31-5)**, both include a heterocyclic ring connected through an amino-methyl link; one of the sulfonamides in each is replaced by a carbon-based acid moiety. The synthesis of the first of these drugs begins with the chlorosulfonation-ammonolysis reaction sequence starting with 2,4-dichlorobenzoic acid (**30-1**). For reasons that are not immediately evident, the chlorine *para* to the sulfonamide group is preferentially activated over that at the *ortho* position toward nucleophilic aromatic displacement. Reaction with furfurylamine (2-methylaminofuran) (**30-3**) thus leads to **furosemide (30-4)** [29].
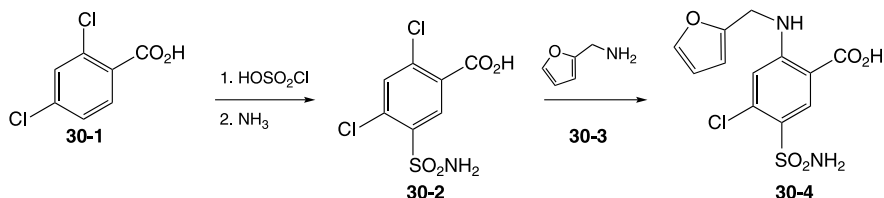
In an analogous scheme, chlorosulfonation of substituted benzonitrile (**31-1**) followed by ammonolysis of the product gives sulfonamide (**31-2**). The regiochemistry of the next reaction, nucleophilc aromatic displacement, can be attributed in this case to the better leaving group properties of fluoride ions over chloride ions. Reaction with 2-methylaminothiophene (**31-3**) thus gives (**31-4**) as the product. There is ample precedent to indicate that tetrazoles are bioisosteric with carboxylic acids, with the two groups showing quite comparable pKAs. Treatment with sodium azide and hydrochloric acid leads to 1,3 addition of the elements of hydrazoic acid
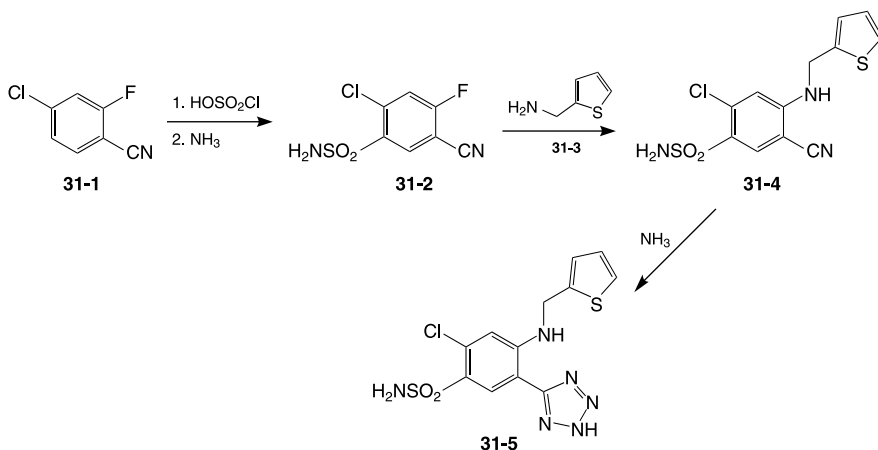
to the nitrile and the formation of a tetrazole ring. This yields the high ceiling diuretic agent **azosemide** (**31-5**) [30].

2.3.3. Oral Hypoglycemic Agents

The peptide hormone insulin is intimately involved in glucose turnover. Disruptions in insulin levels or insulin receptors are manifested as diabetes. So-called juvenile onset diabetes results from a failure to secrete adequate levels of the hormone; this form of the disease, also dubbed insulin-dependent diabetes, is treated by the administration of insulin itself. The far more common form of the disease, which typically strikes in middle age, may be due to a number of causes that result in either insufficient levels of insulin or decreased responses of cellular insulin receptors. This disease, also known as non-insulin-dependent diabetes (NIDD), can be treated by strict diets, by administration of insulin, or, most conveniently, with a series of drugs that lower the elevated glucose levels due to insulin deficiency. The first effective drugs for controlling Type II diabetes were arylsulfonylureas, which also trace their parentage to the sulfonamide anti-bacterials and the clinical observation that high doses of sulfa drugs tended to lower blood sugar. The principal mode of action is believed to involve stimulation of insulin release by pancreatic beta cells.

A number of different routes are available for the preparation of **tolbutamide** (**32-3**), the first oral hypoglycemic agent to be used clinically. The shortest route involves the simple addition of *para*-toluenesulfonamide (**32-1**) to butyl isocyanate (**32-2**) [31]. An alternate route is required for the preparation of a drug that includes a tertiary urea nitrogen. The same starting material (**32-1**) is converted to its carbamate (**32-4**) with ethyl chloroformate in the presence of a base. Heating that intermediate with hexamethyleneimine leads to the displacement of the ethoxy group and the formation of **tolazemide** (**32-5**) [32].
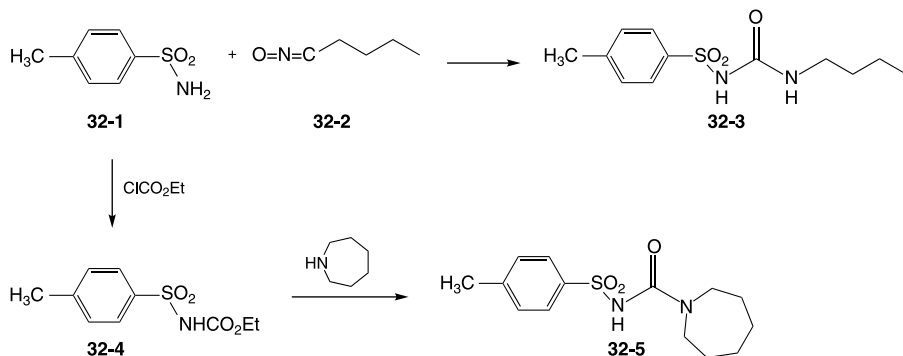
The very low potency of first-generation sulfonylureas required the daily intake of doses measured in grams. The incorporation of complex side chains on the

sulfonyl-bearing benzene ring led to orders of magnitude increases in potency. (This was memorialized by the Upjohn trade name Micronase® for **glyburide**.) Reaction of the acetamide (**33-1**) from 2-phenethylamine with chlorosulfonic acid results in the formation of the *para* sulfonyl chloride; ammonolysis of that intermediate followed by base-catalyzed removal of the acetamide gives the free phenethylamine (**33-2**). This is then acylated with the acid chloride from salicylate (**33-3**) to give the amide (**33-4**). Condensation of this product with cyclohexyl isocyanate gives the sulfonylurea **glyburide** (**33-5**) [33].
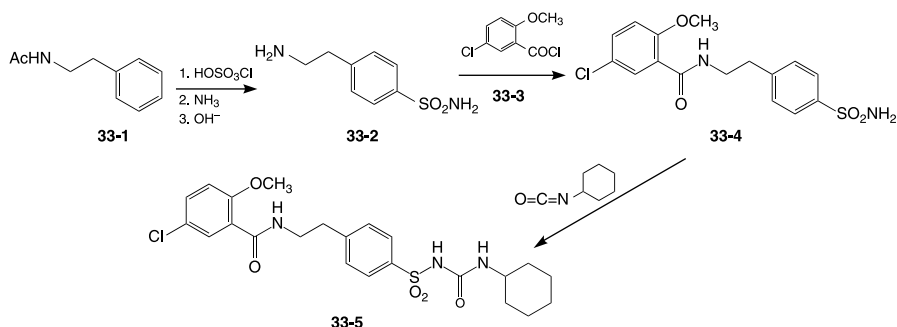
There is evidence from further investigation of the SAR (Structure Activity Relationship) in this series that the sulfonylurea function does not need to be attached to an aromatic ring. The synthesis of this compound starts with a nitrogen interchange between substituted piperidine (**34-1**) and sulfamide. The phthaloyl protecting group (Phth) is then removed by reaction with hydrazine to afford the primary amine (**34-2**). Acylation with the 2-methoxynicotinyl chloride (**34-2**) gives the corresponding amide (**34-4**). Nitrogen interchange between the sulfonamide group in (**34-4**) and the urea function in a bridged bicyclic reagent (**34-5**) results in the displacement of diphenylamine from the reagent and the formation of a sulfonylurea function. There is thus obtained **gliamilide** (**34-6**) [34].
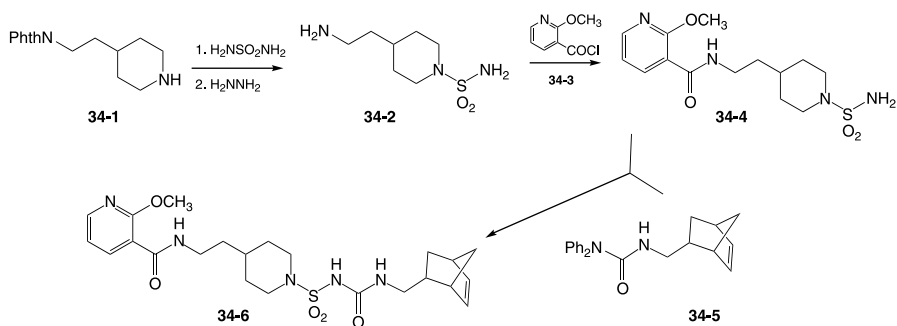
Oral hypoglycemic activity is interestingly retained when the urea function is replaced by what is essentially a cyclic guanidine moiety embedded in a pyrimidine ring. Acylation of substituted 2-aminopyrimidine (**35-2**) with the product (**35-1**) from the reaction of methyl phenylacetate with chlorosulfonic acid gives the sulfonamide (**35-2**). The terminal ester is then hydrolyzed and the resulting acid converted to an acid chloride with thionyl chloride (**35-4**). Reaction of this last intermediate with the substituted aniline (**35-5**) leads to the hypoglycemic agent **gliacetanile** (**35-6**) [35].
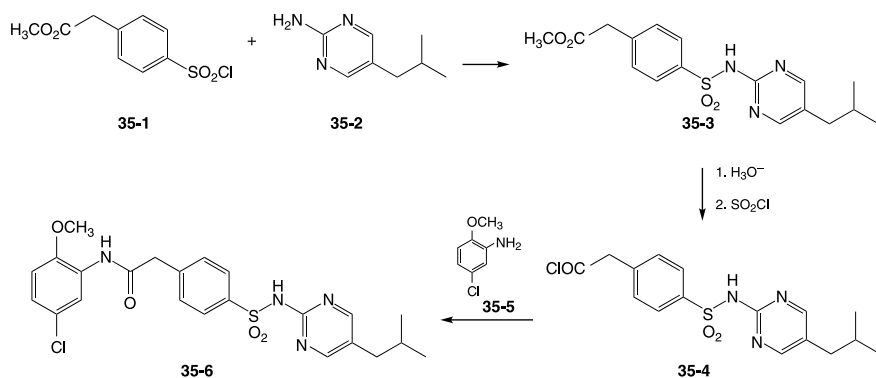
Subsequent research led to the discovery that the sulfonylurea function could be replaced by a thiazoline-2,4-dione group. Though not sulfonamides, these agents are included at this point for the sake of coherence. The mechanism of action of these very potent drugs is distinct from that of their forerunners, which act by stimulating the release of insulin. The class, often referred to as "glitazones," acts on peroxisome proliferator activated receptors (PPAR$_\gamma$) to decrease resistance to insulin. They are thus particularly useful in treating patients with decreased insulin responses. The synthesis of one of these agents starts by condensing benzaldehyde with the mono-oxime (**36-1**) from biacetyl. This undergoes Polonovsky rearrangement on treatment with phosphorus oxychloride, in effect chlorinating the methyl group adjacent to the N-oxide (**36-3**; see Chapter 8 for the mechanism) [36]. Reaction of this intermediate with the anion from the substituted ethyl benzoylacetate (**36-4**) leads to the displacement of halogen from (**36-3**). Heating the first-obtained product in acid leads to the hydrolysis of the ester as well as the aldehyde acetal at the *para* position; the beta-ketoacid decarboxylates under reaction conditions to afford (**36-5**). Base catalyzed of that product with rhodanine (**36-6**) leads to aldol condensation to afford (**36-7**). Catalytic hydrogenation then reduces the double bond to afford the antidiabetic agent **darglitazone** (**36-8**) [37].
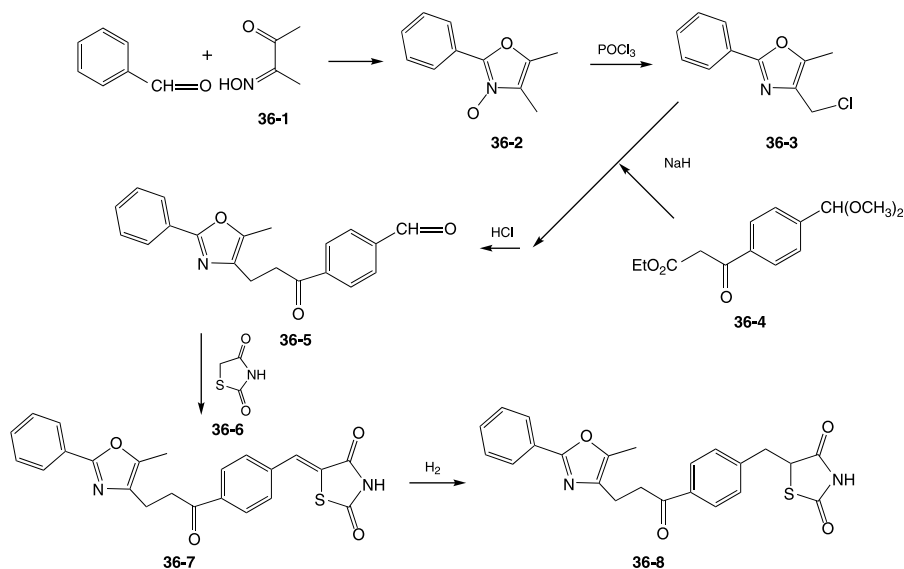
Chromanol (**37-1**), which in essence comprises a cyclic acetal of 3-hydroxy-propylbenzaldehyde, is available in several steps from the corresponding chromone. Reaction of that compound with benzylmagnesium chloride leads to an addition to the latent aldehyde and thus the formation of (**37-2**). Reaction of the crude product with toluenesulfonic acid leads to the cyclodehydration product, chroman (**37-3**). The organometallic reagent from the metal-halogen exchange of (**37-3**) with butyl lithium is then treated with carbon dioxide to afford an acid (**37-4**) on workup. This acid is then resolved by separating the diastereomeric salts formed with a chiral base. The acid from the desired form is then reduced to afford the aldehyde (**37-5**) as a single enantiomer. Aldol condensation with rhodanine (**36-6**)
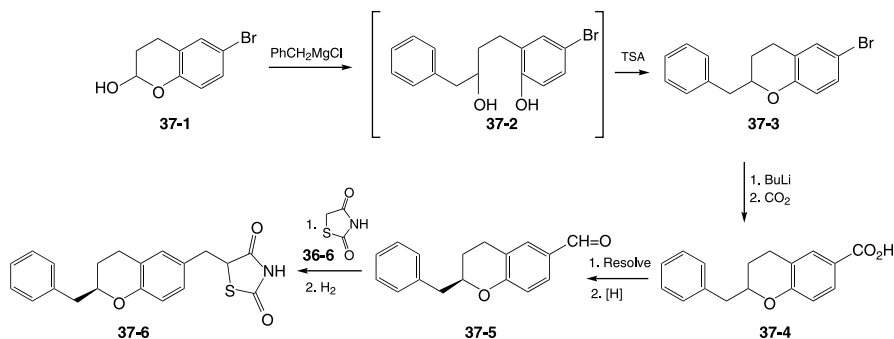
followed by reduction of the double bond in the first product then affords **englitazone** (**37-6**) [38].

Research targeted specifically at PPAR has led to several novel hypoglycemic agents quite unrelated structurally to either the sulfonylureas or the later glitazone antidiabetic agents. The synthesis of the first of these starts with the formation of the enamide (**38-3**) from tyrosine (**38-1**) and 2-benzoylcyclohexanone (**38-2**). Treatment of that product with palladium on charcoal leads to the dehydrogenation of the eneamide ring with consequent aromatization (**38-4**). Condensation of the terminal hydroxyl group on the side chain in the substituted oxazole (**38-5**) with the phenol function on (**38-4**) in the presence of triphenyl phosphine and diethyl azodicorboxylate (DEAD) leads to the formation of an ether bond. This affords the hypoglycemic agent **farglitazar** (**38-6**) [39].
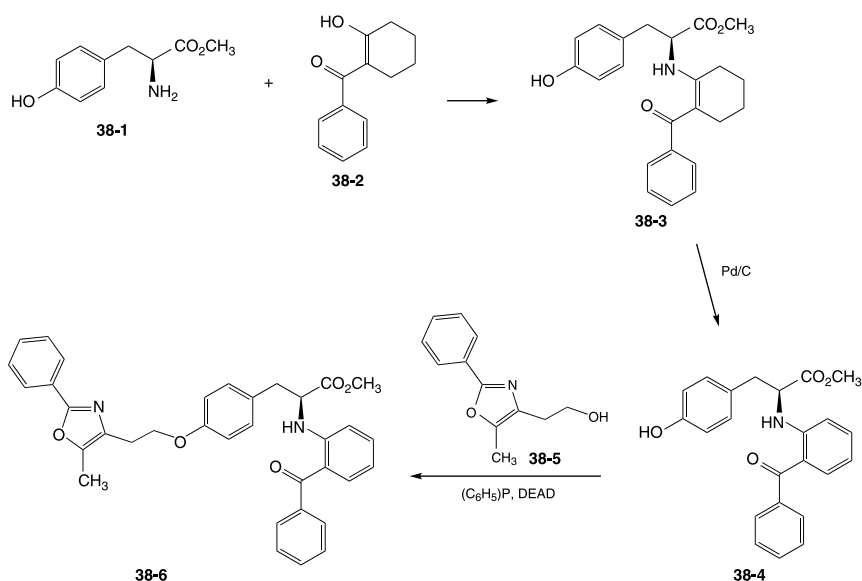
An aryl carbamate replaces the tyrosine moiety in a related analogue. The preparation of this compound involves, first, the activation of the side chain oxygen in the same oxazole used above by conversion to its mesylate (**39-1**) by means of methanesulfonyl chloride. This intermediate is then used to alkylate the phenol group on *para*-hydroxybenzaldehyde (**39-2**). Condensation of the aldehyde group in (**39-3**) with glycine methyl ester leads to the corresponding imine. Reduction of that function with borohydride then gives the intermediate (**39-4**). Acylation of the amino group in that compound with *para*-anisyl chloroformate (**39-5**) then gives **muraglitazar** (**39-6**) [40].
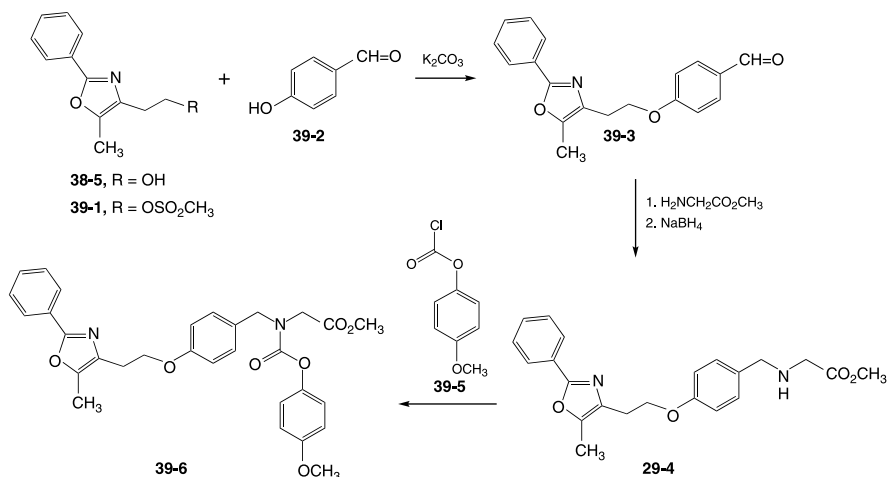
2.3.4. Miscellaneous Arylsulfonamides

The incorporation of a perchloroethylene side chain interestingly leads to a di-sulfonamide that is used as a veterinary antiparasitic agent. Reaction of *meta*-nitro(perchloroethyl)benzene (**40-1**) with iron powder in acid, as expected, reduces the nitro group to an aniline; the reagent in addition removes two chlorine atoms from the side chain to give the corresponding olefin (**40-2**). Subjecting that intermediate to the standard chlorosulfonation followed by an ammonolysis sequence then adds two sulfonamide groups to yield **clorsulon** (**40-3**) [41].
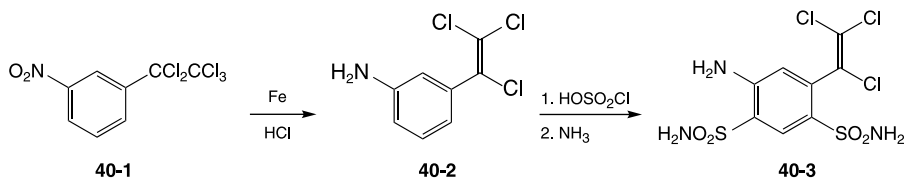
As noted in the discussion on the arachidonic acid cascade in Chapter 1, thromboxane A_2 (TXA$_2$), one of the products from that cascade, is one of the most potent known platelet-aggregating and inflammatory substances. Though cyclooxygenase inhibitors, such as the NSAIDs, do decrease levels of TXA$_2$, these agents often exhibit deleterious effects on the GI tract. A pair of structurally closely related compounds that contain sulfonamide moieties has recently been described that competes with TXA$_2$ for its binding sites and thus offers the possibility of more specific drug action. Preparation of **daltroban** (**41-3**) involves

the formation of the sulfonamide by reaction of the primary amine in (**41-2**) with *para*-chlorobenzenesulfonyl chloride (**41-1**). Synthesis of an analogue that is arguably more readily accessible starts with the alkylation of the phenol group in (**41-4**) with ethyl bromoacetate in the presence of a base. Hydrolysis of the alkylation product with strong acid removes both the amide and ester groups to yield a free amino acid (**41-5**). This is converted to its benzenesulfonamide as above but using instead unsubstituted benzenesulfonyl chloride to afford **sulotroban** (**41-6**) [42].
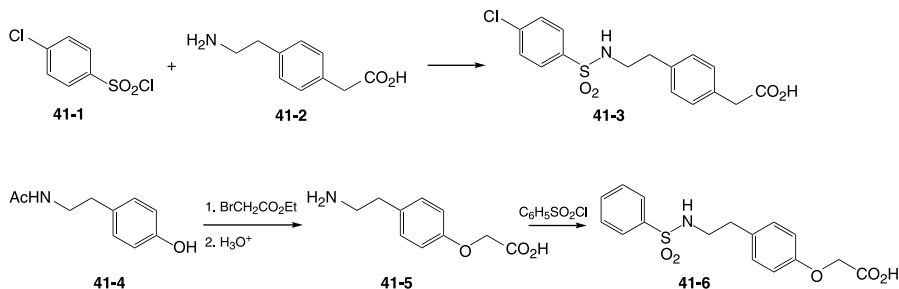
2.4. ARYLACETIC AND ARYLPROPIONIC ACIDS

The anti-inflammatory and antipyretic salicylates and pyrazoles were among the first synthetic organic drugs to find extensive clinical use. Their widespread use led to a growing awareness of the side effects associated with these drugs, particularly when used in the high doses required for alleviating the symptoms of osteoarthritis. The finding that arylacetic and arylpropionic acids showed the same activity led to intensive research in the area and the introduction of dozens of new NSAIDs. All of these compounds share the same mechanism of action: inhibition of the arachidonic acid cyclooxygenases (COXs). It should be noted in passing that these drugs act indiscriminately against all variants of the enzymes COX-1, COX-2, as well as possibly COX-3. As a result, the agents also inhibit the formation of prostaglandin-stimulated stomach-protecting mucus, thus producing gastric side effects.

2.4.1. Arylacetic acid "Fenacs"

The prototype for this class of compounds is **ibufenac** (**42-3**), developed by a group at Boots in the UK. This drug was to be quickly superseded by its α-methylated congener, **ibuprofen**, from the same laboratory [43]. The mechanistically very complex Wilgerodt reaction constitutes the key to the preparation of **ibufenac**. Thus, reaction of the acetylation product (**42-1**) from isobutyl benzene and acetyl chloride with sulfur and morpholine leads to the transposition of the oxidized function to the terminal carbon and formation of thiomorpholide (**42-2**). Hydrolysis of the thioamide

in acid results in the concomitant replacement of sulfur by oxygen to give a carboxylic acid. There is thus obtained **ibufenbac** (**42-3**).

Both the potency and duration of action are markedly increased by the addition of appropriate substituents to the benzene ring. The routes for preparing such compounds differ markedly from that use to prepare **ibufenac**. The synthesis of one of the more widely prescribed NSAIDs in this class, **diclofenac** (**43-5**), in essence involves a sequence for walking a substituent over onto the ring from an adjacent nitrogen. The sequence starts with the careful acylation of diphenyl-amine (**43-1**) with one equivalent of oxalyl chloride. A Friedel–Crafts ring closure of the thus obtained acid chloride (**43-2**) leads to isatin (**43-3**). The two carbonyl groups in that compound differ in that one is an amide while that next to the benzene ring has more ketone-like reactivity. Treatment of the isatin with hydrazine and potassium hydroxide under Wolff–Kischner conditions effects the reduction of the ketone function and the formation of the lactam (**43-4**). Hydrolysis of the amide function then affords the amino acid **diclofenac** (**43-5**) [44].

Good activity is interestingly retained when a carbonyl group is added to the ring and the aniline becomes primary. The synthesis of two of these agents resembles that the one mentioned above by involving an intermediate indolone ring. The starting *N*-amino-2-indolone (**44-1**) can be obtained by reduction of the *N*-nitrosation product of indolone itself. Reaction of this intermediate, which is in essence an *N*-acylhydrazine, with phenylacetone (**44-2**) gives the corresponding hydrazone (**44-3**). The hydrazone is then treated with ethanolic hydrogen chloride; Fischer indole formation would in theory lead initially to the fused bicyclic indole (**44-4**). The observed product (**44-5**) can be rationalized by assuming that the labile bicyclic *N*-acyl indole opens to an ester in the presence of ethanolic hydrogen chloride. Ozonization of the double bond in the heterocyclic ring then leads to *N*-acylated benzophenone (**44-6**), with the acetyl group arising from the ring atom bearing a methyl group. Acid hydrolysis of that intermediate removes both the amide and the ester group to afford **amfenac** (**44-7**) [45].
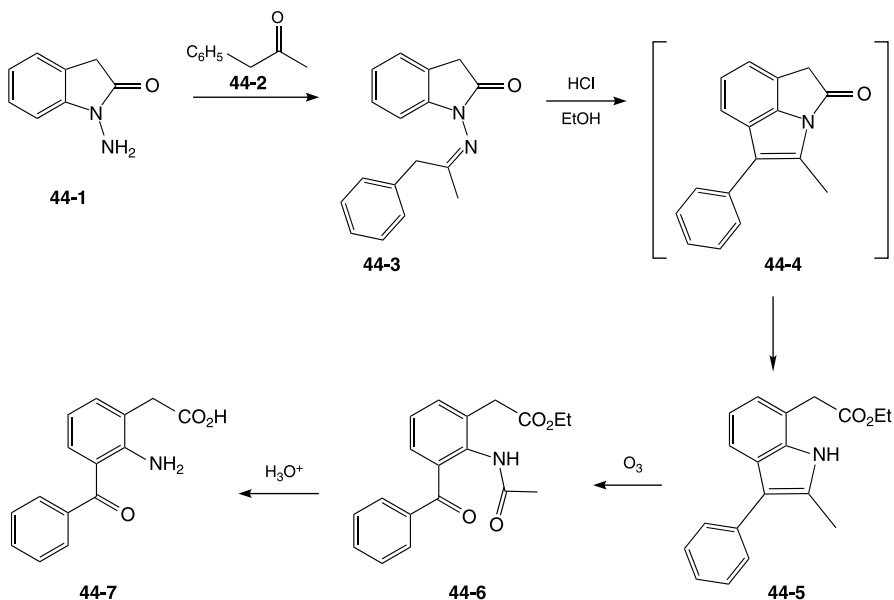
Construction of the closely related NSAID **bromefenac** (**46-8**) depends on the Gassman indolone synthesis [46] for incorporation of the acetic acid chain. That reaction involves an anion-initiated electrocyclic rearrangement related conceptually to the little-known Hauser *ortho* substitution rearrangement. The simplest example of the latter depends on the formation of a carbanion by abstraction of one of the acidic protons from a benzyltrimethyl quaternary salt to give **I** (the

abstraction of a more acidic benzyl proton gives a stable anion that simply reverts to the starting material). The resulting anion then adds to the aromatic ring to start the electrocyclic reaction depicted below (**I** → **II**); the net effect after bond reorganization (**III**) is migration of a dimethylaminomethyl group to the *ortho* position.
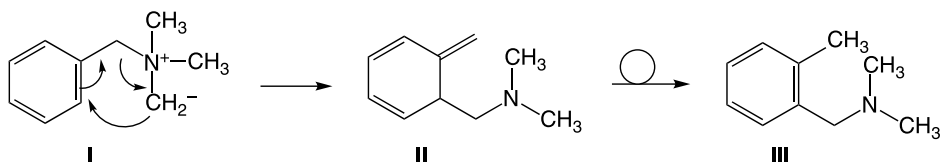
The key sulfonium reagent (**46-2**) for the Gassman synthesis is obtained by chlorination of ethyl 2-thiomethylacetate (**46-1**). The displacement of chlorine from that reagent by nitrogen in the aminobenzophenone (**46-3**) gives the corresponding sulfonium salt (**46-4**). The reaction proceeds with a surprisingly mild base. Thus the anion (**46-5**) from the treatment of (**46-4**) with triethylamine adds to the benzene ring and can start an electrocyclic reaction analogous to that the one mentioned above. The initial product (**46-6**) is not observed. Instead, triethylamine is a sufficiently stronger base than aniline to ionize the latter. The product from that process would then displace ethoxide from the adjacent ester group to give the observed indolone (**46-7**). The thiomethyl group is then removed with Raney nickel; hydrolytic cleavage of the amide completes the synthesis of **bromfenac** (**46-8**) [47].
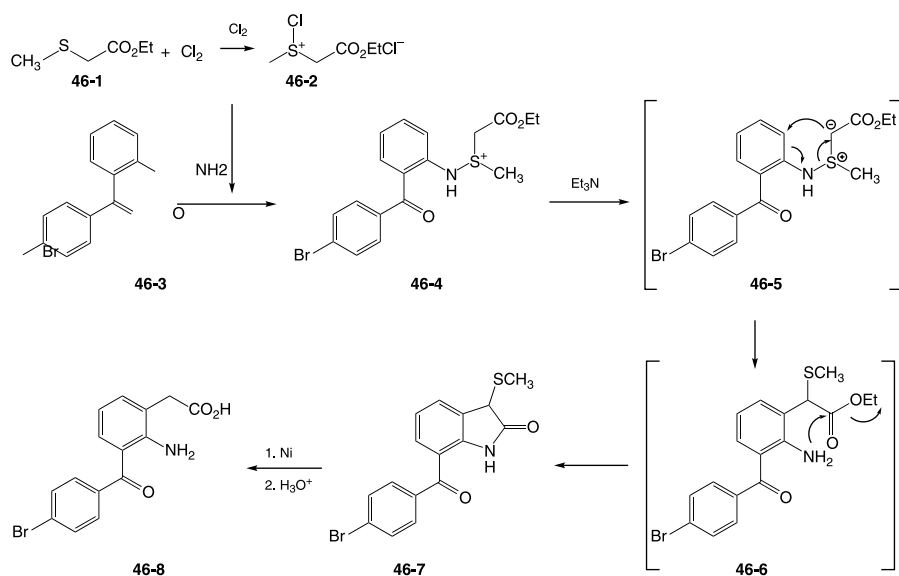
2.4.2. Arylpropionic Acid "Profens"

Further work on the arylacetic acids by investigators at Boots revealed that the incorporation of a methyl group on the acid chain improved the potency of **ibufenac** (**42-3**). The resulting NSAID, **ibuprofen** (**47-4**), very quickly found very widespread use since it showed improved potency and tolerance over aspirin, which had for decades been the mainstay drug for the same indications. Direct methylation of the carbanion from (**42-3**) would seem at first sight to be an attractive route to this drug. In practice, however, this reaction leads to a difficultly separable statistical mixture of the desired product, a *bis*-alkylated by-product and the starting material. Conversion of the acetate side chain to a malonate blocks over-alkylation and at the same time facilitates deprotonation. Thus, reaction of the ethyl ester (**47-1**) from **ibufenac** with diethyl carbonate in the presence of sodium ethoxide leads to the malonate carbanion (**47-2**). This is not isolated, but quenched *in situ* with methyl iodide to give the alkylation product (**47-3**). The malonate is then hydrolyzed in acid; the free malonic acid decarboxylates under reaction conditions afford **ibuprofen** (**47-4**) [48].
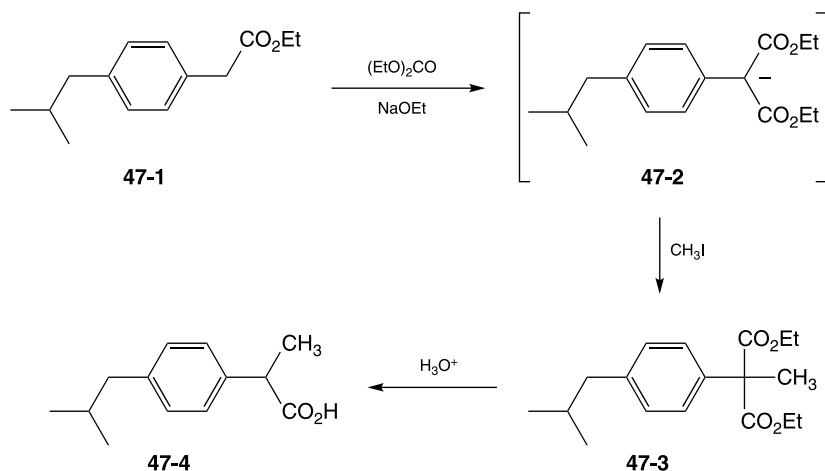
The huge demand for this drug combined with the relatively high dosage, which can amount to grams per day, led to intense efforts to develop other synthetic approaches. One of the several alternate schemes for preparing this compound involves a modification of the Darzens glycidic ester synthesis. Addition of the carbanion from the treatment of 2-chloroacetonitrile with sodium ethoxide to ibufenac intermediate (**48-1**) leads initially to the adduct (**48-2**). As in the Darzens reaction, the alkoxide displaces chloride on the adjacent carbon to form an epoxide to give the observed product (**48-3**). Treatment of that intermediate with a Lewis acid such as lithium perchlorate leads to an opening of the oxirane ring with concomitant hydrogen migration. There is thus obtained the α-cyanoketone (**48-4**), a structure that may be viewed as a variant on an acid chloride. Treatment with aqueous base converts that intermediate to **ibuprofen** (**47-4**) [49].
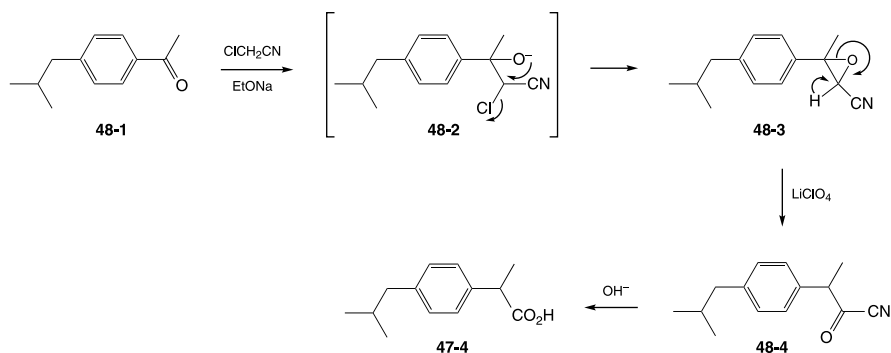
An interesting variant on the Wilgerodt reaction offers a simple three-step procedure that avoids the wastage involved in the schemes above, which require the incorporation of an extra carbon atom that must later be eliminated. The sequence starts with the acylation of isobutylbenzene (**49-1**) with propionyl chloride to give propiophenone (**49-2**). Reaction of that with thallium III nitrate and methyl *ortho*-formate in methanol leads in high yield to the methyl ester (**49-3**) of **ibuprofen** [50]. This would be the method of choice for preparing the drug but for two unfortunate facts: the extreme toxicity of thallium and the very high sensitivity of analytical methods for the detection of metals. It proved to be virtually impossible, in practice, to produce samples that showed zero residues of thallium.
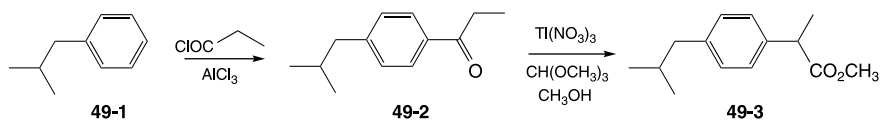
Yet a further increase in potency is observed when the *para*-isobutyl group is replaced by a benzene ring. One published synthesis for that compound is quite analogous to the malonate route to the parent drug. The acetyl biphenyl (**50-1**) is thus converted to the corresponding arylacetic acid by reaction with sulfur and morpholine, followed by hydrolysis of the first-obtained thiomorpholide. This is then esterified and converted to malonate anion (**50-2**) with sodium ethoxide and ethyl formate. The anion is quenched with methyl iodide; hydrolysis of the esters followed by decarboxylation yields the NSAID **flubiprofen** (**50-3**) [51].
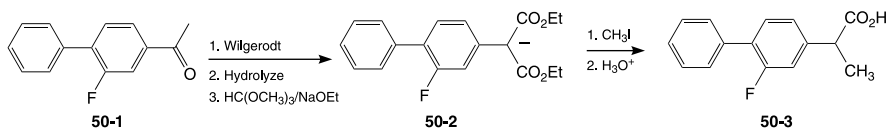
It of interest to note that the isobutyl group may also be replaced by a heterocyclic ring. The route to this compound, **pirprofen** (**51-6**), starts with the direct methylation of unesterified 4-nitrophenylacetic acid (**51-1**). The observed selectivity for monoalkylation in this case may reside in the structure of the dianion, whose most stable form is presumably that depicted in (**51-2**). Catalytic reduction of the product (**51-3**) gives the corresponding aniline; this is then converted to its acetanilide (**51-4**) with acetic anhydride. Treatment with chlorine followed by hydrolysis gives the chloroaniline (**51-5**). Double alkylation of this last intermediate with 1,4-dichlorobut-2-ene (depicted as the *cis* isomer for aesthetic reasons) forms the dihydropyrrole ring. There is thus obtained the NSAID **pirprofen** (**51-6**) [52].
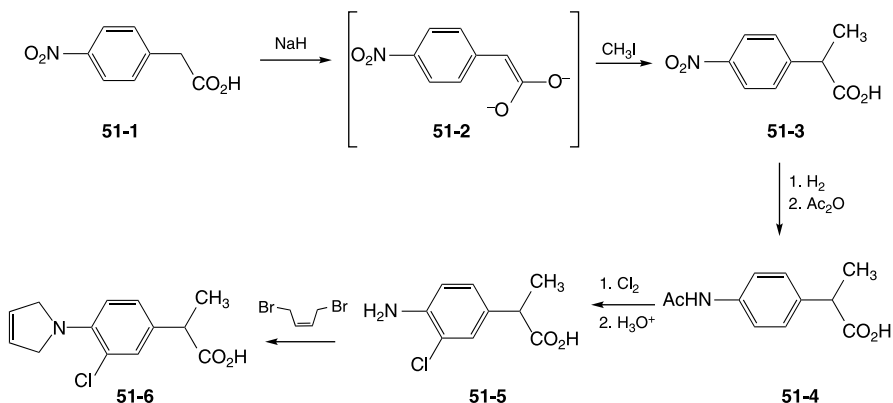
The rather different scheme used to prepare the propionic acid side chain in **cicloprofen** (**52-5**) leads to the inclusion of this tricyclic compound in the present chapter, which is intended to deal with monocyclic compounds. The synthesis starts with the Friedel–Crafts acylation of the hydrocarbon fluorene (**52-1**), with the half-ester of oxalyl chloride to give the α-ketoester (**52-2**) as the product. The required side chain methyl group is then added by reaction of the product with methylmagnesium bromide; this apparently proceeds selectively
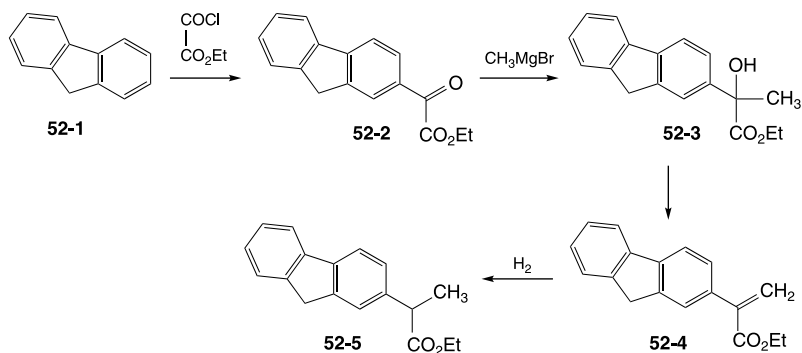
at the ketone function to give the tertiary carbinol (**52-3**). The benzylic tertiary alcohol readily dehydrates on treatment with acid to a methylene group (**52-4**). Catalytic reduction of this last intermediate followed by hydrolysis of the ester leads to **cicloprofen** (**52-5**) [53].

The fact that the profen NSAIDs owe their activity to the inhibition of the cyclo-oxygenase enzymes would lead to the expectation that the activity would reside in mainly a single enantiomer since one of those should more closely fit an interacting site in the chiral enzyme than the other. The enzyme is of course asymmetric as a consequence of the chiral amino acids of which it is composed. Extensive work has demonstrated that the activity of NSAIDs is due in virtually all cases to the *S* enantiomer. It has also been shown, as an interesting side-light, that the less active *R* isomers of many NSAIDs are converted *in vivo* to their *S* enantiomers. The emphasis on developing drugs that consist of active enantiomers has prompted the development of technology for producing single isomers. This is of course more economical than the resolution of a racemate since the latter process implies discarding at least 50% of the product. A scheme for producing pure *S* ketoprofen provides a good example of stereospecific reduction [54]. Only the last of the several schemes for introducing the chiral center located at the side chain methyl group offers a method for controlling the enantiomeric identity for that position. Several asymmetric Wilkinson-type catalysts that are chiral by reason of binaphthyl asymmetry are available commercially. Reduction of the α-methylene-substituted *meta*-benzylphenyl-acetic acid (**53-1**) in the presence of BINAP[2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)] leads to a single isomer of the propionic acid (**53-2**). Oxidation of the benzyl group to a ketone gives *S*-(+)-**ketoprofen** (**53-3**). (Attempted reduction of the corresponding methylene ketoprofen is said to give far inferior selectivity.)
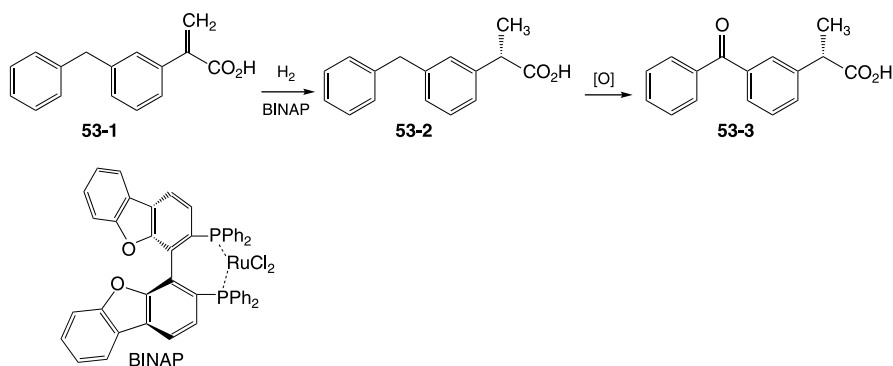
2.4.3. Arylacetamide Antiarrhythmic Compounds

The chemistry of antiarrhythmic drugs derived conceptually from sotalol was described at the outset of this chapter. An earlier, small series of drugs that are used clinically as antiarrhythmic agents is based on alkylated derivatives

of phenylacetamide. The first of these, **disopyramide** (**54-5**), bears an interesting structural resemblance to the opioid analgesic **methadone** (**54-6**), which represents the ultimate structural simplification of morphine. Both compounds incorporate the minimal structural requirements for opioid activity posited by the Becket–Casey rule: a tertiary nitrogen atom at the equivalent of two carbon atoms removed from an aromatic ring attached to a quaternary center (see Chapter 7 for a more detailed discussion of opiate analgesics). The syntheses for these antiarrhythmic drugs rely heavily on carbanion alkylation chemistry. The synthesis of the first of these drugs starts with the nucleophilic aromatic displacement of bromine in 2-bromopyridine (**54-2**) by the carbanion from phenylacetonitrile (**54-1**) to give the intermediate (**54-3**). Alkylation of the carbanion from that product with *N,N*-diisopropyl-2-chloroethylamine gives the highly substituted nitrile (**54-4**). Hydrolysis of this product with sulfuric acid stops at the amide stage to give **disopyramide** (**54-5**) [55].
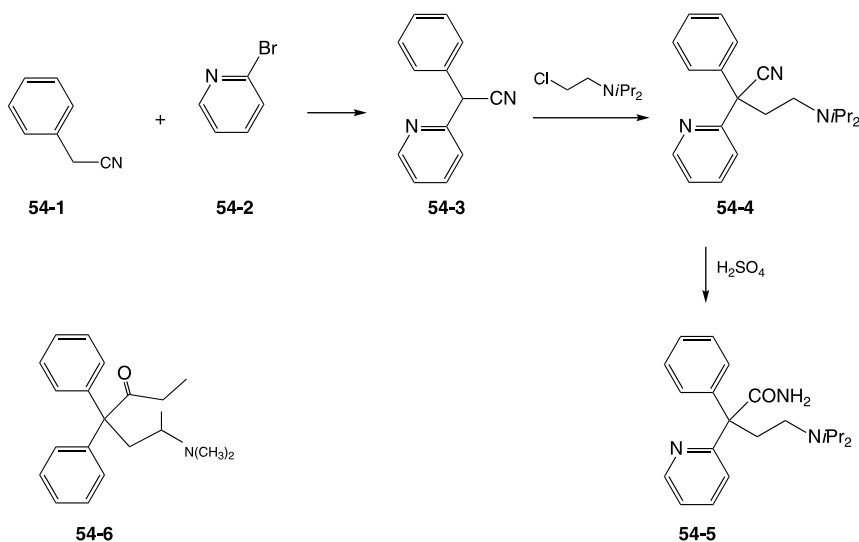
Replacement of the pyridine ring by a more strongly basic ethylpiperidine moiety leads to the antiarrhythmic drug **disobutamide** (**55-5**). The synthesis of this compound also involves successive carbanion alkylation reactions. Thus, reaction of the anion from *ortho*-chloroacetonitrile (**55-1**) with *N*-(2-chloroethyl) piperidine gives the intermediate (**55-3**); alkylation of the anion from this leads to (**55-4**). Hydrolysis with sulfuric acid completes the preparation of **disobutamide** (**55-5**) [56].
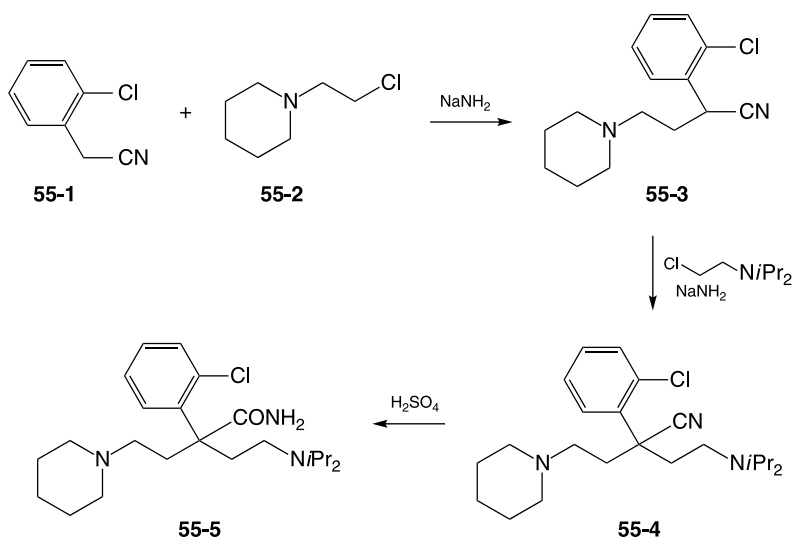
One of the more common pathways for the metabolic transformation of tertiary amines involves *N*-dealkylation to a secondary amine. The observation that those products often show the same biological activity as the parent drug in many cases confounds the issue of the identity of the chemical species responsible for the drug's action. The fact that the dealkylation product of **disobutamide** shows antiarrhythmic activity in its own right prompted the synthesis of the acetyl derivative of that secondary amine; this agent may be considered a latent form of the active metabolite. This compound is prepared by first repeating the penultimate step in the **disobutamide** synthesis using (*N*-benzyl-*N*-isopropyl)-2-chloroethylamine instead of the diisopropyl intermediate. The product from that reaction (**56-1**) is then hydrolyzed to the
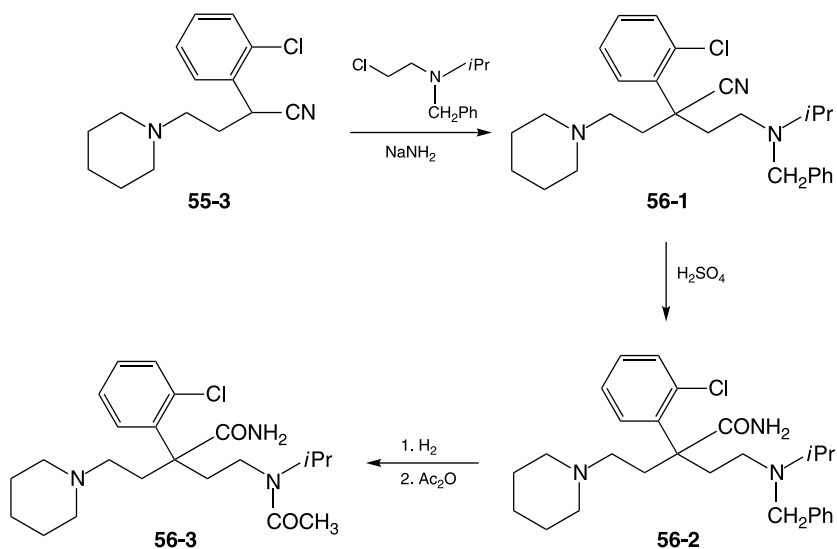
amide with sulfuric acid. The sequential hydrogenolysis of the benzyl group in the resulting amide (**56-2**), followed by acetylation of the secondary amine with acetic anhydride, gives **bidisomide** (**56-3**) [57].

2.5. LEUKOTRIENE ANTAGONISTS

The fatty acid-like leukotrienes derived from the addition of glutathione to products of the lipoxygenase branch of the arachidonic cascade are closely associated with manifestations of asthma. Many compounds designed to antagonize leukotrienes at the receptor level incorporate long alkyl chains to mimic the leukotrienes backbone in addition to the sulfur-containing moieties that stand in for glutathione. The reaction
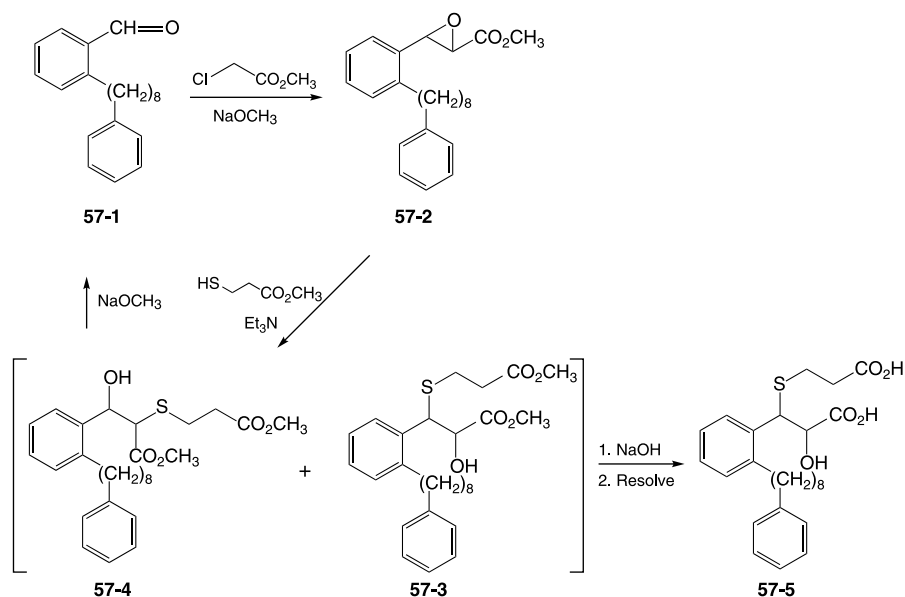
of benzaldehyde (**57-1**) (note that the benzene rings are separated by eight methylene groups) with methyl chloroacetate and sodium methoxide in a classic Darzens reaction leads to the glycidic ester (**57-2**). The mercaptide from methyl 3-merapto-propionate with a base opens the oxirane in by attack at either end, leading to a pair of regioisomers (**57-3** and **57-4**). Treatment of the mixture with sodium methox-ide causes the isomer (**57-4**) to undergo reverse aldol condensation and to thus regen-erate the starting aldehyde (**57-1**); the isomeric product (**57-3**) is stable under reaction conditions. Isolation of (**57-3**) followed by saponification of that product and the subsequent resolution of the resulting free acid via its salt with α-phenethylamine affords **pobilukast** (**57-5**) [58].

The structure of the leukotrienes receptor antagonist **cinalukast** (**58-9**) bears only the vaguest resemblance to its predecessor, or, for that matter, to a leukotriene. Reaction of the cyanomethylphosphonate (**58-1**) with hydrogen sulfide converts the nitrile to a thioamide (**58-2**). Treatment of that intermediate with the bromoketone

(**58-3**) leads to formation of a thiazole (**58-4**) in a fairly general procedure for building that heterocyclic ring (see Chapter 8). This intermediate forms an ylide under surprisingly mild conditions. Thus reaction of the phosphonate with *meta*-nitrobenzaldehyde (**58-5**) in the presence of potassium carbonate leads to the coupling product (**58-6**) as the expected *trans* isomer. The nitro group is then reduced to the corresponding amine (**58-7**) by means of stannous chloride. Reaction of this last intermediate with 2,2-diethyl succinic anhydride (**58-8**) leads to an attack by the amine on the sterically more accessible carbonyl group, leading to **cinalukast** (**58-9**) [59].
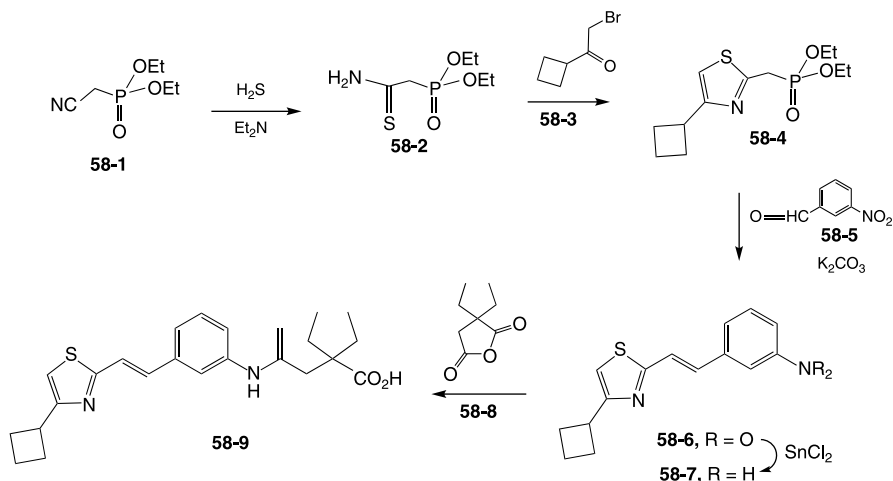
The antiasthamtic activity of the sulfur-free substituted long chain fatty acid **seratrodast** (**59-5**) is attributed to the antagonism of thromboxanes, whose structures also include a fatty side chain, rather than to leukotrienes. Friedel–Crafts acylation of benzene with the acid chloride from monomethyl pimelate (**59-1**) leads to
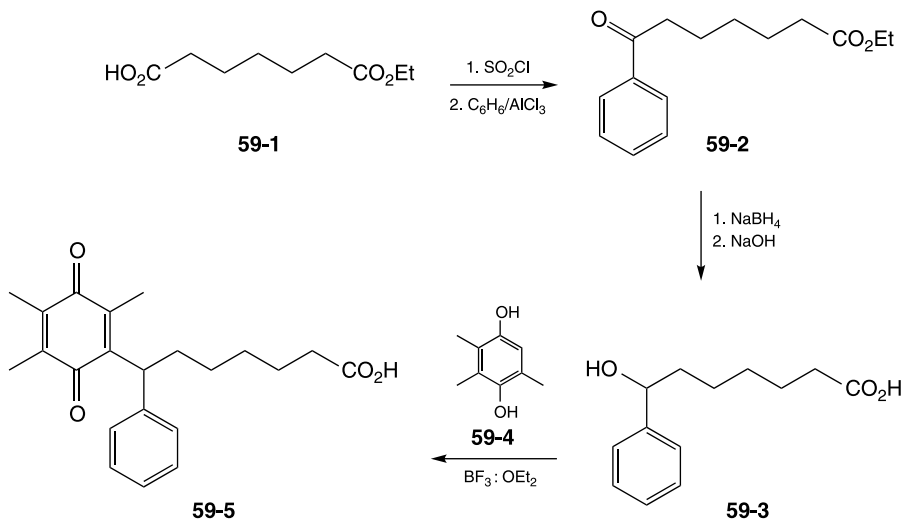
the keto acid (**59-2**). The ketone is then reduced to the alcohol with borohydride; saponification affords the corresponding hydroxyl acid (**59-3**). Treatment of that intermediate with the hydroquinone (**59-4**) in the presence of boron trifluoride probably results initially in loss of the hydroxyl group to form the benzylic carbocation. This then attacks the electron-rich hydroqinone ring to form the coupling product. The newly added ring oxidizes to a quinone either in the course of the reaction or on workup to afford **seratrodast** (**59-5**) [60].

The bronchodilating activity of theophylline, one of the mainstays for treating asthma, is now known to be a result of the inhibition phosphodiestease enzymes (PDEs; see Chapter 15). Research over the past several decades has revealed that PDEs in fact comprise a series of closely related substances that interact with distinct receptors. Compounds that act as inhibitors at specific PDE sites associated with lung function offer better tolerated drugs than theophylline. A small series of catechol ethers has provided bronchodilators that act largely against PDE-4. Alkylation of the catechol benzaldehyde (**60-1**) with cyclopentyl bromide affords the corresponding ether (**60-2**). This is converted to methyl ketone (**60-3**) by the addition of methyl lithium followed by oxidation of the first-obtained carbinol by means of pyridinium chlorochromate (PCC). Reaction with hydroxylamine leads to oxime (**60-4**); the oxime hydroxyl is then converted to a carbamate by one of several methods as, for example, by reaction with trimethylsilyl isocyanate to afford filaminast (**60-5**) [61].

Oxidation of the aldehyde group in mixed ether (**60-2**) by means of perchlorate affords the corresponding carboxylic acid. That product is then converted to its acid chloride (**60-6**) with thionyl chloride. Treatment of this last intermediate with the substituted pyridine (**60-7**) leads to the corresponding amide and thus **piclamilast** (**60-8**) [62].
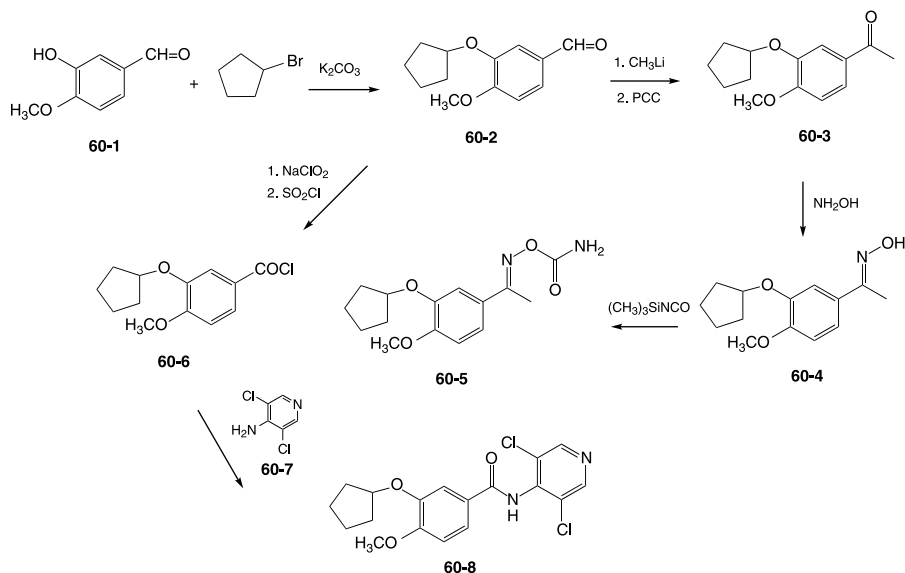
A relatively simple benzamide inhibitor of phosphodiesterase 4 has proven to be useful for treating chronic pulmonary obstructive disease (COPD). The synthesis

of this compound begins by alkylation of the free phenol on aldehyde (**61-1**) with chlorodifluromethane in the presence of a base to afford mixed ether (**61-2**). Oxidation of the carbonyl group with hypochlorite followed by reaction with thionyl chloride leads to the acid chloride (**61-3**). Condensation of that last intermediate with the same substituted aminopyridine as above (**60-7**) affords the benzamide **roflumilast** (**61-4**) [63].
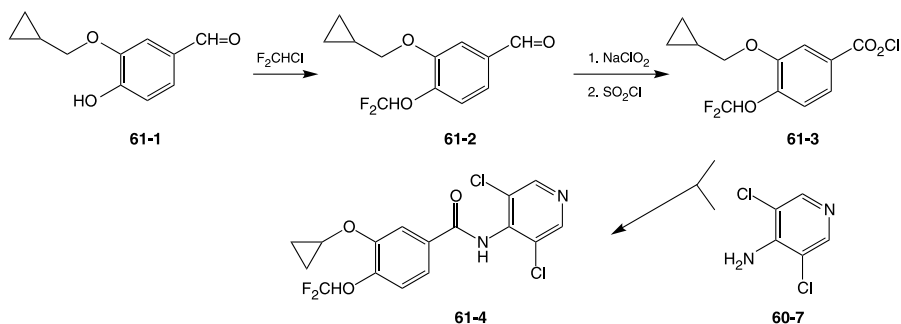
2.6. MISCELLANEOUS COMPOUNDS

A structurally very simple carboxylic acid, **modafinil** (**62-4**), increases alertness and inhibits narcolepsy as a result of its activity as a cerebral α_1-adrenergic agonist. The short synthesis begins with the reaction of benzhydrol proper (**62-1**) with chloroacetic
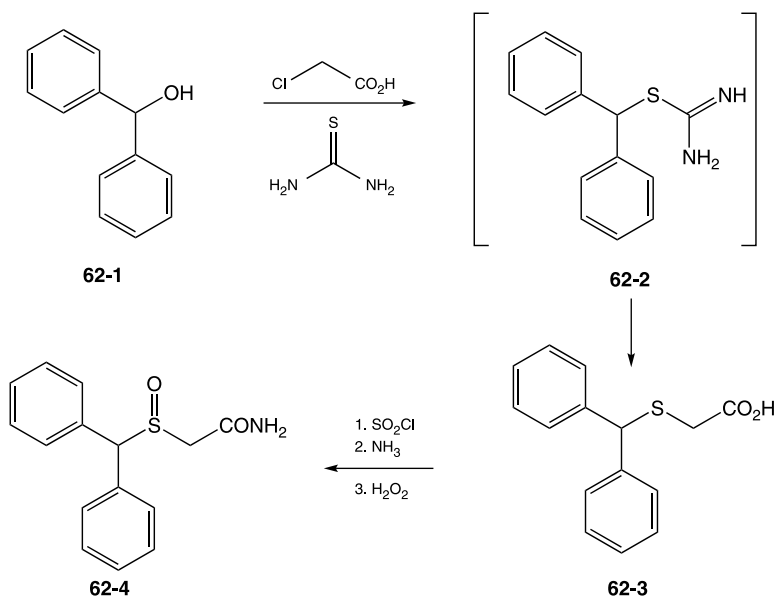
acid in the presence of thiourea. The reaction takes an unusual course in that sulfur has replaced oxygen on the benzhydryl carbon. The initial step may involve the

intermediacy of a thiouronium compound such as (**61-2**). The overall product from this reaction (**62-3**) is then converted to the amide by sequential reactions with thionyl chloride and then ammonia. The oxidation of sulfur with hydrogen peroxide leads to the sulfoxide and thus **modafinil** (**62-4**) [64].

Carbanion alkylation reactions play an important role in the synthesis of a pair of calcium channel-blocking agents used in the treatment of angina caused by insufficient blood supply to cardiac muscle. The activity on the coronary vasculature of the first of these compounds, **verapamil** (**63-5**), was recognized over 30 years ago; elucidation of the detailed mechanism of action, however, awaited recognition of the role of cellular calcium channels on vascular tone. A first step in the convergent synthesis consists in the alkylation of homoveratrylamine (**63-1**) with 1-bromo-3-chloropropane to give (**63-2**); alkylation of the carbanion from dimethoxyphenyl-acetonitrile (**63-3**) with isopropyl bromide gives (**63-4**). A recent modification of the last alkylation step involves phase transfer catalysis-like conditions; thus, the reaction of (**63-2**) and (**63-4**) with solid powdered sodium hydroxide and potassium carbonate and sodium iodide in toluene in the presence of tetrabutylammonium bromide affords **verapamil** (**63-5**) [65].
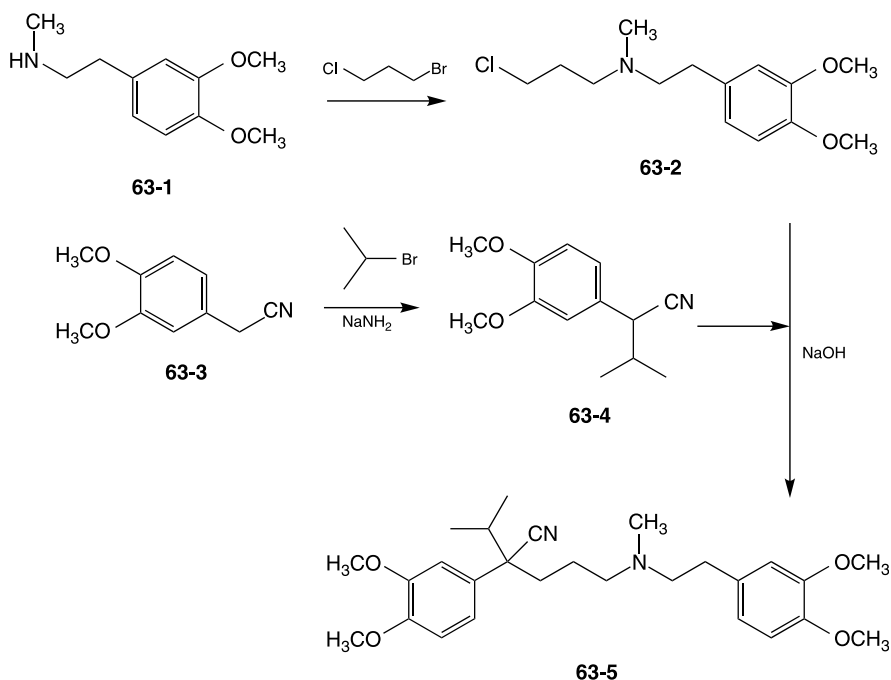
A modification on **verapamil** uses a spiro-dithiane moiety to supply the quaternary center. Reaction of veratraldehyde (**64-1**) with propane 1,3-dithiol leads to dithiane (**64-2**). Reaction with hydrogen peroxide oxidizes the ring sulfur atoms to

the corresponding sulfones (**64-3**), providing a reagent suitable for an umpolung-like reaction. Thus, alkylation of the carbanion from the now quite acidic aldehyde derivative with a **verapamil** intermediate (**63-2**) gives the antianginal agent **tiapamil** (**64-4**) [66].
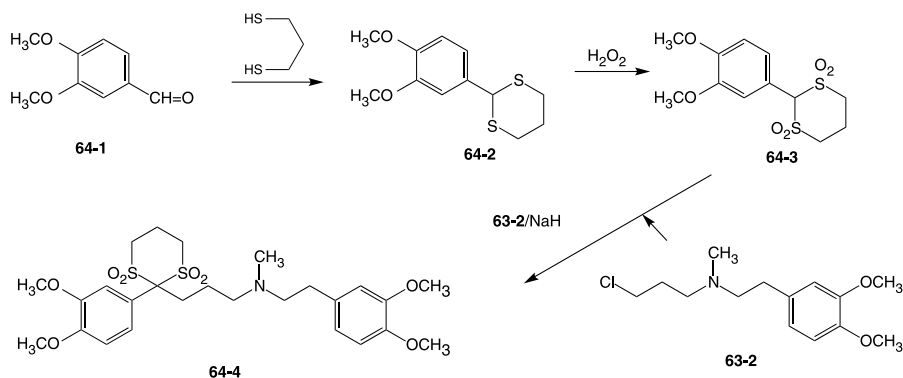
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CHAPTER 3

INDENES, NAPHTHALENES, AND OTHER POLYCYCLIC AROMATIC COMPOUNDS

Chapter 2 illustrated cases in which benzene rings served as structural elements in drugs whose functions ranged from forming part of a pharmacophore to simply providing a framework to support needed functionality. Much the same is true for fused carbocyclic ring systems. These ring systems may serve, for example, as surrogate substituted benzene rings. The extra fused ring in **propranolol** (**1-1**) provides bulk at the *ortho* position to the oxypropanolamine side chain for that β-blocker. In much the same vein, the indene ring system in the hypoglycemic agent **glyhexamide** (**1-2**) replaces the benzene ring found in many other sulfonylureas of this class. The present chapter focuses on classes of drugs characterized by polycyclic systems as well as some that illustrate interesting synthetic methods.
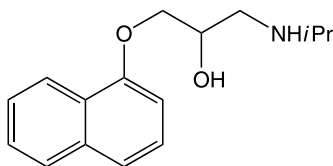
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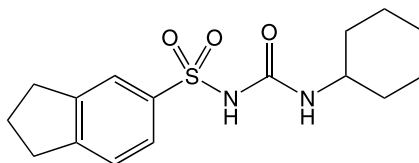
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3.1. INDENES

It is now widely recognized that the majority of drugs owe their action to binding with receptors on target organ cells. The shape of such a ligand will be expected to have a direct effect on binding efficiency since the binding configuration of receptors exists in relatively defined three-dimensional arrangements. A molecule that closely complements the shape of a receptor would be expected to bind more efficiently than one that needs to undergo conformational changes prior to binding. This provides the rationale for preparing so-called rigid or constrained analogues, molecules that are locked in those close-fit conformations.

The acryloyl ketone side chain of the non-thiazide "high ceiling" diuretic agent, **ethacrynic acid** (**2-1**), can rotate quite freely; the *ortho* chloro substituent would in fact be expected to favor an orthogonal arrangement to avoid a nonbonding interaction. An analogue of this compound, in which the motion of that side chain is constrained, **indacrinone** (**2-8**), interestingly shows slightly better activity than the parent. Direct comparison is complicated by the fact that the two agents show different electrolyte and urate excretion patterns. The synthesis starts with the Friedel–Crafts acylation of 2,3-dichloroanisole (**2-2**) with phenylacetyl chloride (**2-3**) to give a ketone (**2-4**). The side chain exomethylene group is then introduced by Mannich reaction with the preformed carbinolamine from formaldehyde to give (**2-5**). Reaction of this product with concentrated sulfuric acid leads to internal alkylation to form indanone (**2-6**). Reaction of the ketone with a strong base and then methyl iodide leads to the alkylated product (**2-7**). Demethylation of the methyl ether with a strong acid affords the corresponding phenol (**2-8**). The phenoxide ion from the treatment of that product with a base is then alkylated with ethyl bromoacetate. Saponification of the ester leads to the free acid an **indacrinone** (**2-8**) [1].
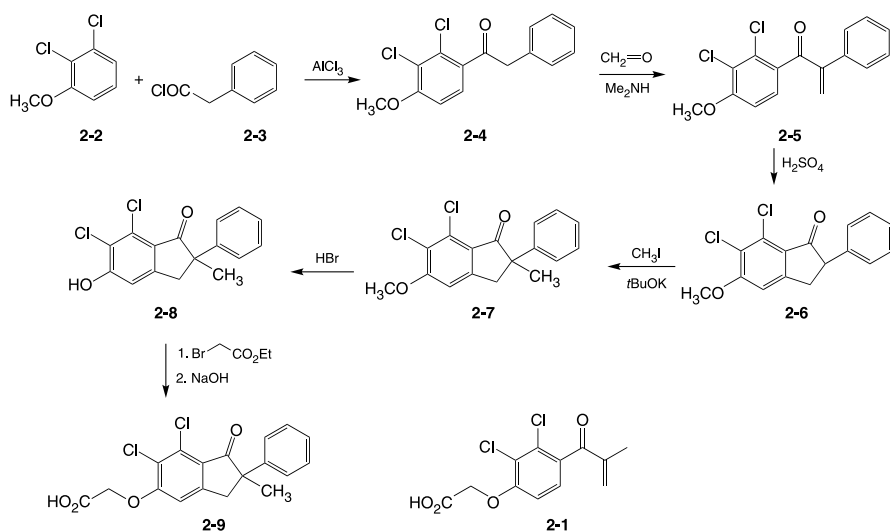
Yet another illustration of the importance of steric considerations for biological activity comes from the finding that the indene **sulindac** (**3-8**) shows qualitatively the same anti-inflammatory activity as the older NSAID compound, **indomethacin** (**3-1**). The indanone ring in intermediate (**3-3**) is formed by internal Friedel–Crafts acylation of acid (**3-2**) by means of polyphosphoric acid. Reformatskii reaction on that ketone with methyl bromoacetate and zinc leads to the addition to the carbonyl group and the formation of tertiary carbinol (**3-4**). This readily dehydrates to the corresponding indene (**3-5**) on treatment with *para*-toluenesulfonic acid. The protons on the remaining benzylic position are reasonably acidic due to the potential stabilization of an anion by the adjacent olefin and benzene rings. Thus reaction of (**3-5**) with *para*-thiomethylbenzaldehyde (**3-6**) in the presence of sodium methoxide leads to the formation of a condensation product; hydrolysis of the ester then gives (**3-7**) as a mixture of isomeric olefins in which the Z isomer predominates. Isolation of that isomer followed by oxidation of sulfur by reaction with sodium metaperiodate completes the synthesis of **sulindac** (**3-8**) [2]. There is evidence to indicate that the proximate active agent is in fact the sulfide (**3-7**) that is formed by an unusual metabolic reduction of the sulfone in (**3-8**).
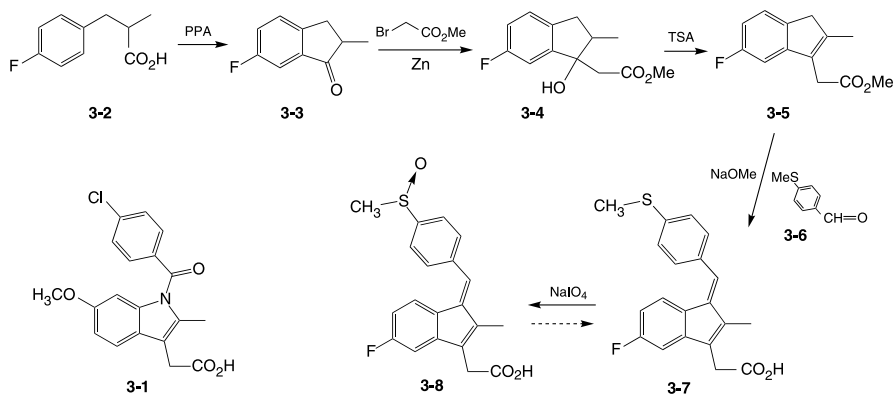
The medicinal chemistry of Alzheimers is complicated by the fact that the etiology of this disease is still far from clear. Evidence points to an association with decreased levels of acetyl choline in the brain. Many of the drugs that have been introduced to date for treating this disease thus comprise agents intended to raise the deficient levels of that neurotransmitter by inhibiting the loss of existing acetylcholine due to the action of cholinesterase. A compound based on an indene that, perhaps surprisingly, inhibits that enzyme has been proposed for the treatment of Alzheimer's. Aldol condensation of piperidine aldehyde (**4-2**) with the indanone (**4-1**) from cyclization of 3,4-dimethoxycinnamic acid leads to the olefin (**4-3**). Catalytic reduction removes the double bond to afford **donepezil** (**4-4**) [3].
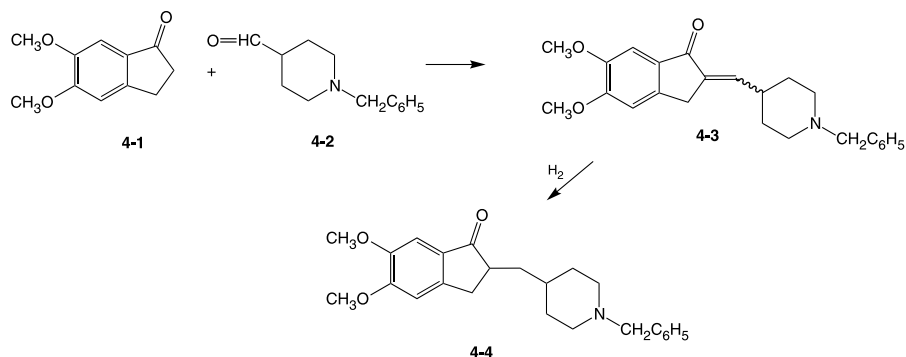
More recent work indicates that monoamine oxidase (MAO) inhibitors may also be useful in treating Alzheimers. The indene **ladostigil** (**5-5**) is intended to address both those targets; the compound thus incorporates both a carbamate group associated with anticholinesterase activity and a propargyl moiety found in MAO inhibitors. The synthesis involves juggling protecting groups on two reactive functions. Thus, reaction of amino-indanol (**5-1**) with *bis-tert*-butoxy carbonate affords the corresponding BOC protected derivative (**5-2**). Treatment of that derivative with *N*-methy-*N*-ethyl carbamoyl chloride affords the *O*-acylated carbamate (**5-3**). The BOC protecting group is then removed by means of hydrogen chloride to give the free amine (**5-4**). Reaction of this last with propargyl bromide gives **ladostigil** (**5-5**). This drug consists of a single (*R*) enantiomer; it is not clear from the source [4] at which stage the resolution takes place.
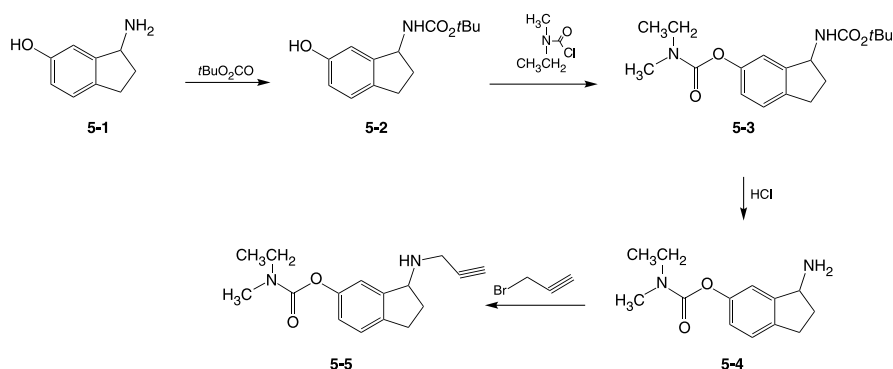
The endogenous hormone atrial natriuretic peptide (ANP), which acts to increase blood pressure, is, like many other effector peptides, excised from a longer native chain by an endopeptidase enzyme, that is, an agent that cleaves bonds well along the chain of amino acids. A small-molecule endopeptidase inhibitor lowers blood pressure by inhibiting the release of ANP. The inhibitor **candoxatril** (**6-8**) is now

approved as an antihypertensive agent. Reaction of the half-ester of substituted mal-onate (**6-1**) with formaldehyde in pyridine adds a formyl group to the α-position. That transient intermediate loses the elements of carbonic acid under reaction conditions to afford the exomethylene derivative (**6-2**). Treatment of that acrylate with the dianion from cylopentylcarboxylic acid (**6-3**) leads to conjugate addition of the anion on carbon and formation of the chain extended acid (**6-4**). The free acid is then coupled with *cis*-4-aminocyclohexane protected as its benzyl ester (**6-5**) to afford the amide; exposure of the product to trifluoroacetic acid cleaves the *t*-BOC ester to afford the acid (**6-6**). The free acid is then condensed with 5-indanol (**6-7**) to give the corresponding ester. Hydrogenolysis then cleaves the benzyl amine to give the free amine and, thus, **candoxatril** (**6-8**) [5].
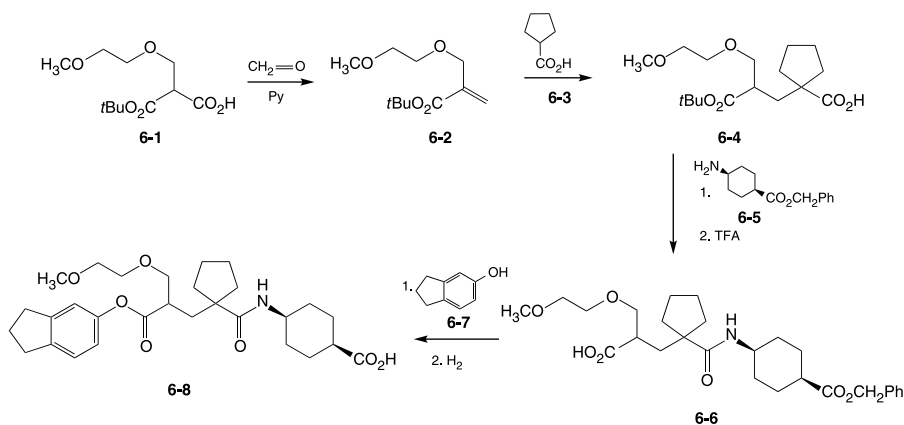
The hormone melatonin (**7-13**) is intimately involved in the diurnal cycle with levels rising late in the day prior to sleep. Anecdotal evidence suggests that some indi-viduals find that compound itself useful for inducing sleep. Congeners have, as a result, been prepared in the search for sleep inducing drugs. **Ramelteon** (**7-12**), an indene that incorporates several structural features present in the hormone, has been approved by the FDA as a sleeping aid. The first part of the synthesis involves the construction of the ethylamine side chain. Thus, the condensation of indanone (**7-4**) with the yilde from 2-diethoxyphoshonoacetonitrile attaches the requisite two-carbon chain (**7-2**). The nitrile is then reduced to the corresponding primary amine my means of Raney nickel (**7-3**). Reduction of the double bond with rhodium in the presence of the chiral catalyst BiNAP (2,2′-*bis*(diphenylphos-phino)-1,1′-binaphthyl) affords the intermediate (**7-4**) as the *S* enantiomer. This is then acylated with propionyl chloride to afford (**7-5**). The remainder of the scheme involves the construction of the fused furan ring. Bromination proceeds at the slightly less hindered position. The methoxy group is then cleaved with boron tribromide to yield the bromophenol (**7-6**). Alkylation of the phenol with allyl bromide proceeds to the allyl ether (**7-7**). Heating that compound leads to a Claisen rearrangement of the

C-allyl derivative (**7-8**); bromine at the other *ortho* position prevents the formation of the alternate undesired isomer. Ozonization followed by reductive workup leads to (**7-9**); treatment of the aldehyde with sodium borohydride reduces that function to an alcohol, providing (**7-10**). The blocking bromine atom is then replaced by hydrogen by means of hydrogenation over palladium (**7-11**). Construction of the furan ring starts by conversion of the primary alcohol to its mesylate with methanesulfonyl chloride. Treatment of the product with triethyl amine forms the phenoxide, which then displaces the mesylate group. This internal displacement forms the furan ring. There is thus obtained **ramelteon (7-12)** [6].
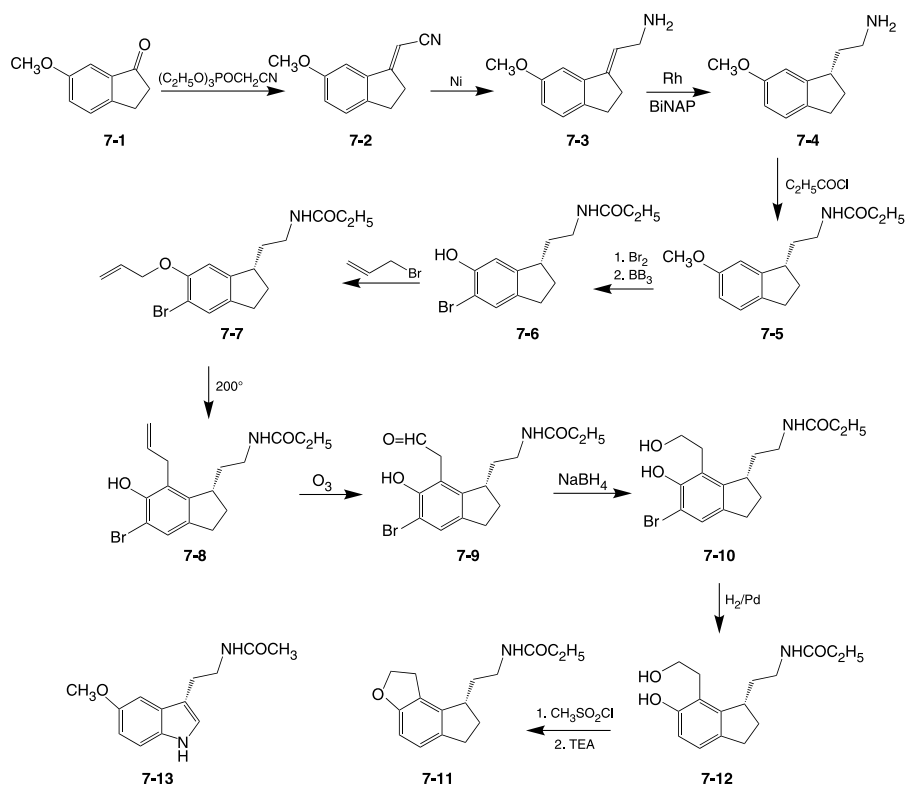
3.2. NAPHTHALENES

3.2.1. Antifungal Agents

Several antifungal drugs that differ markedly in functionality from the large group of imidazole-based "conazole" drugs (Chapter 8) include benzocycloalkane or hydronaphthalene rings. The absence in the literature of simple benzenoid analogues may indicate that the bicyclic moiety plays a role in those drugs' mechanisms of action. Members of the older series all share a thiocarbamate function based on

meta toluidine. The starting material for the synthesis of the first of these, thiocarba-moyl chloride (**8-1**), is obtained in a straightforward fashion by reaction of 2-naphthol with thiophosgene. Treatment of this acid chloride with *N*-methyl-*meta*-toluidine (**8-2**) gives the antifungal agent **tolnaftate** (**8-3**) [7]; wide use of that compound demonstrated the safety and efficacy that led to its approval for use in nonprescription products. The exact analogue prepared from 5-indanol [8], **tolindate** (**8-4**) is reported to be somewhat less potent.
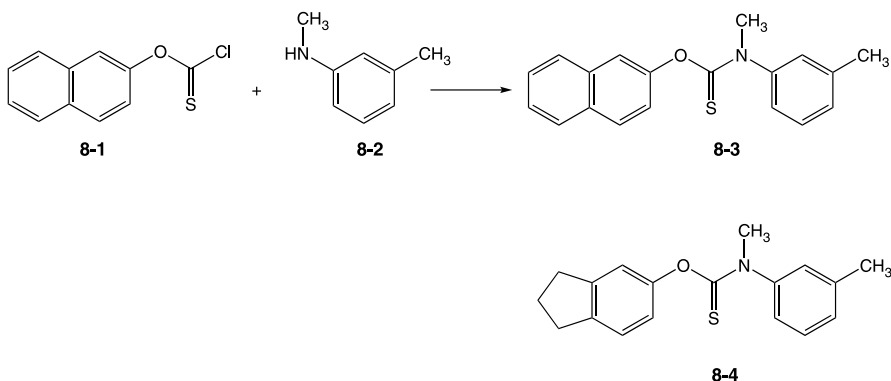
The fused ring in a more complex member of this series, **tolciclate** (**9-7**), combines structural elements from both the naphthalene and indan series. The key step in the preparation of this agent involves Diels–Alder condensation of a substituted benzyne with cyclopentadiene. Reaction of iodo-bromo anisole (**9-1**) can be envisaged to proceed initially to a Grignard reagent-like intermediate such as (**9-2**); this could then undergo internal elimination of magnesium bromoiodide to lead to the highly reactive benzyne (**9-3**). A 1,4-addition across cyclopentadiene will then lead to the observed product, benzonorbornadiene (**9-4**). This isolated olefinic bond in this intermediate is reduced by catalytic hydrogenation; the phenol ether is then cleaved by treatment with hydrobromic acid to give a free phenol (**9-5**). The standard sequence, which consists of a reaction with thiophosgene followed by *N*-methyl-*meta*-toludine, completes the synthesis of **tolciclate** (**9-7**) [9].
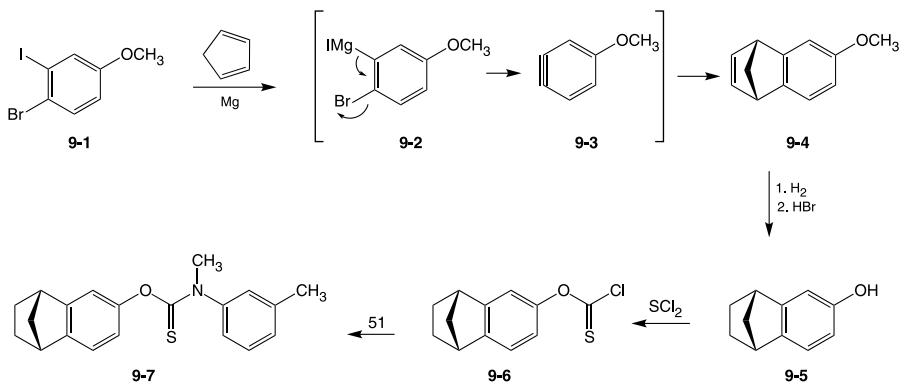
Naphthalenes lacking any functional group beyond a substituted-α-methylallyl-amine group form another small series of antifungal agents. The prototype for this series, **naftidine** (**10-3**), is prepared by simple alkylation of N-methyl-α-methylnaphthylamine (**10-1**) with cinnamyl bromide (**10-2**) [10]. The *trans* geometry of the double bond in the starting material is retained in the product. Replacement of the phenyl group in this compound by *tertiary*-butylacetylene leads to a more potent compound. The preparation this agent begins with the alkylation of the common intermediate (**10-1**) with propargyl bromide. The product (**10-4**) is then coupled with 1-bromo-2-*tertiary*-butylacetylene by means of a copper salt catalyzed reaction in the presence of a mild base such as a *tertiary* amine. Construction of the allylamine function takes advantage of a reaction characteristic of propargyl amines.
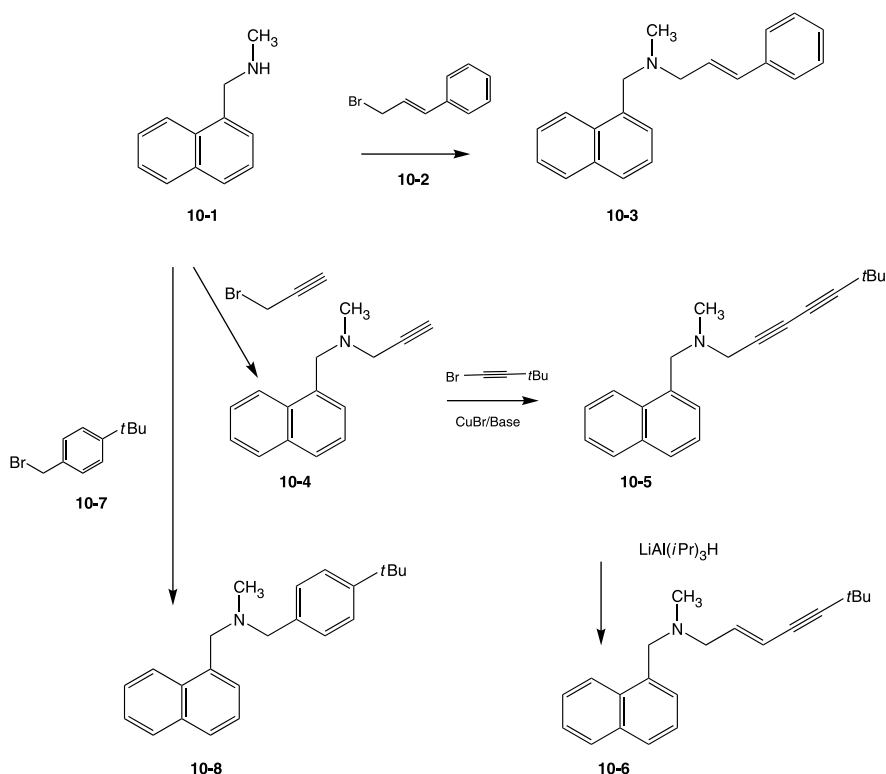
Thus reaction of intermediate (**10-5**) with lithium di-*iso*-propylaluminum hydride proceeds to give a selective reduction of the double bond closest to the amino group; the observed selectivity can be rationalized by assuming the intermediacy of a complex of the hydride reagent with basic nitrogen. There is thus obtained the antifungal agent **terbinafine** (**10-6**) [11]. Anifungal activity is retained when the complex side chain in that compound is replaced by a substituted aromatic ring. Thus alkylation of the ubiquitous naphthylamine (**10-1**) with 4-*tert*-butylbenzyl bromide (**10-7**) affords the antifungal agent **butenafine** (**10-8**) [12].

3.2.2. Miscellaneous Naphthalenes

The antiasthmatic compounds that act via interaction with leukotrienes receptors, discussed in Chapter 2, incorporated structural fragments that mimic the fatty acid that forms the backbone of the target. A relatively simple naphthalene with only a vestigial side chain acts upstream of those compounds by inhibiting the lypoxygenase necessary for the formation of leukotrienes. The naphthalene ring in this compound is assembled via an unusual route that involves the use of a metal carbonyl. The first step involves converting bromobenzene (**11-1**) to its lithio reagent by, for example, a halogen-metal interchange with butyl lithium. Reaction with chromium hexacarbonyl leads to the insertion of one of the carbonyl groups onto the aromatic ring. The base then converts the first-formed product to its enolate (**11-2**). This is then reacted *in situ* with trimethyl oxonium fluoroborate to afford the isolable methyl ether (**11-3**). Reaction of this intermediate with 1-hexyne (**11-4**) in the presence of a base and acetic anhydride affords the product from the insertion of a second carbonyl at the adjacent ring position followed by cycloaddition of the acetylene. The oxygen atom from the second carbonyl insertion is acylated somewhere along the line to afford **bunaprolast** (**11-5**) [13].
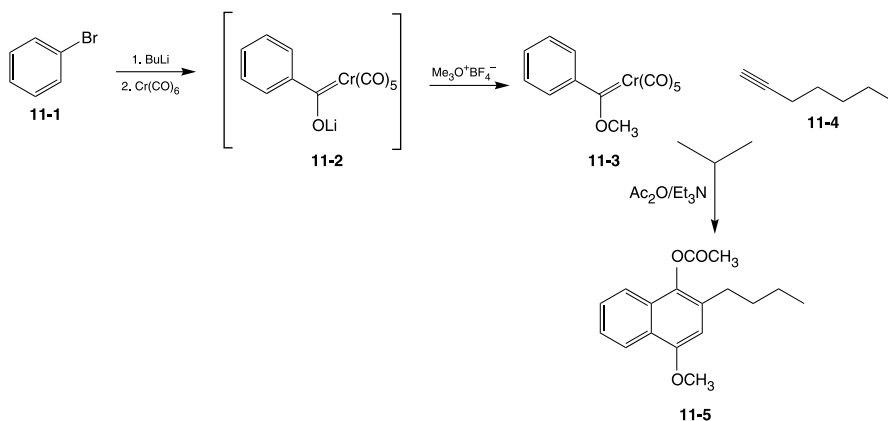
The D (*R*) isomer of the amino acid *N*-methyl aspartate, more familiarly known as NMDA, serves as the endogenous agonist at a number of central nervous system (CNS) receptor sites. This agent is not only involved in neurotransmission, but it also modulates responses elicited by other neurochemicals.

Excessive NMDA receptor stimulation may be implicated in cell death in stroke and in cases of brain injury. Compounds that act as antagonsists at NMDA receptors have, in addition, been found to act as antiepileptic agents. The route to one of the more potent NMDA inhibitors starts by the reaction of naphthylamine (**12-1**) with cyanogen bromide to afford the nitrillamine (**12-2**). Treatment of that intermediate with the aniline (**12-3**) leads to the addition of the amine to the cyano group in (**12-2**) and the formation of the highly substituted guanidine (**12-4**), **aptinagel** [14].

12-1   12-2   12-3   12-4
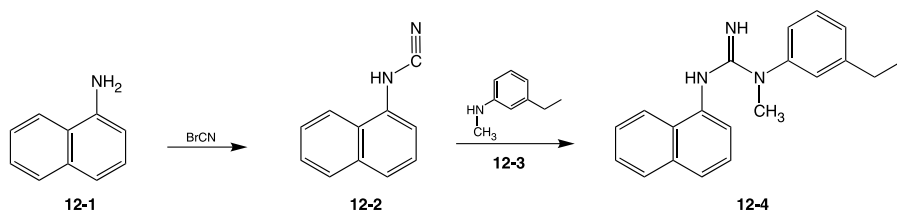
It is now recognized that protein kinases, enzymes that phosphorylate hydroxyl groups on peptides, play an important role in intra- and intercellular communications. These enzymes are consequently intimately involved in cell proliferation. The p38 kinase, for example, regulates the production of key inflammatory mediators. Excess expression of this factor is involved in the pathology of rheumatoid arthritis, psoriasis, and Crohn's disease. A rather structurally complex protein kinase inhibitor that includes a substituted naphthyl moiety has shown preliminary *in vivo* activity. The convergent synthesis starts with the construction of a heterocyclic fragment. Condensation of the keto-nitrile (**13-1**) with *para*-tolylhydrazine (**13-2**) proceeds to give the pyrazole (**13-3**). The overall transform can be rationalized by the initial formation of a hydrazone; addition of the remaining hydrazine nitrogen to the nitrile would then form the pyrazole ring. Reaction of this intermediate with phosgene then converts the primary amine to an isocyanate (**13-4**). The other branch of the synthesis involves, first, the alkylation of the BOC protected naphthylamine (**13-5**) with chloroethyl morpholine (**13-6**) in the presence of a base. Exposure to acid then cleaves the BOC group to afford the free amine (**13-7**). The addition of the amino

13-1   13-2   13-3   13-4

13-5   13-6   13-7

13-8
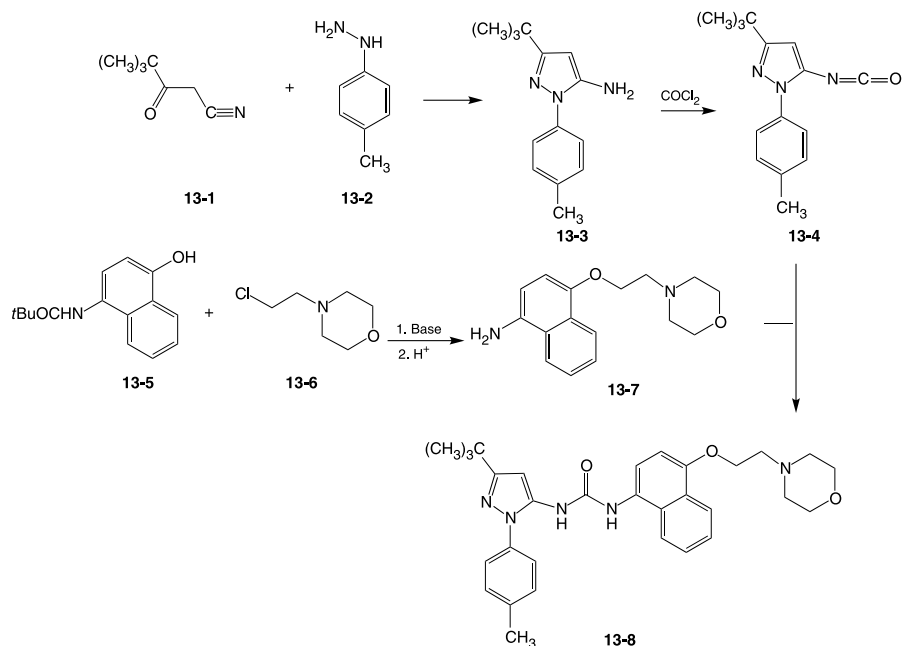
group in this intermediate to the reactive iscocyanate in (**13-4**) connects the two halves via a newly formed urea function. There is thus obtained the p38 kinase inhibitor **doramapimod** (**13-8**) [15].

3.3. PARTLY REDUCED NAPHTHALENES

3.3.1. Bicyclic Retinoids

The effects on cell proliferation of retinoids have led to investigations of analogues of the natural compounds as potential agents for treating not only diseases of the skin but also as potential antineoplastic drugs. Much of the earlier work dealt with analogues in which the polyene chain terminated in a cyclohexene (Chapter 1). It has since been found that the activity was retained and perhaps enhanced by fusing an aromatic ring onto the cyclohexene; the distal unsaturation in those cases is provided by the fused benzene ring. The breadth of the structural tolerance in this class of compounds is suggested by the fact that all but one of the five double bonds can be replaced by aromatic rings. It is of note that the terminal carboxyl group can be replaced by a methylsulfonyl function, a moiety that is quite polar but one whose pK is orders of magnitude removed from that of a carboxylic acid. The construction of this compound also demonstrates a reversal of the strategy used to prepare pelretin (Chapter 1), in which the nucleus provides the ylide. The synthesis starts with the acylation of tetramethyltetralin (**14-1**) with acetyl chloride in acetic anhydride to give (**14-2**). Successive reduction with sodium borohydride to the alcohol, conversion to a bromide (**14-3**), and, finally, displacement of halogen with triphenylphosphine gives the phosphonium salt (**14-4**). Condensation of the ylide obtained from this compound with *para*-methylsulfonylbenzaldehyde (**14-5**) leads directly to **sumarotene** (**14-6**) [16].
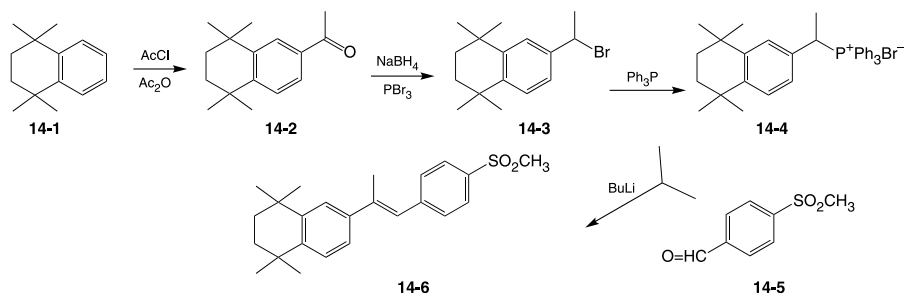
Activity on cell proliferation is maintained when a major part of the side chain is replaced by an amide linkage. The tetralin-based compound **tamibarotene** (**15-7**) has been tested as an agent for treating leukemias. Reaction of the diol (**15-1**) with hydrogen chloride affords the corresponding dichloro derivative (**15-2**). Aluminum chloride-mediated Friedel–Crafts alkylation of acetanilide with the dichloride affords the methylated tetralin (**15-3**). Basic hydrolysis then leads to the primary

amine (**15-4**). Acylation of the primary amino group with the half-acid chloride, half-ester from terephthalic acid (**15-5**) leads to the amide (**15-6**). Basic hydrolysis of the ester grouping then affords **tamibarotene** (**15-7**) [17].
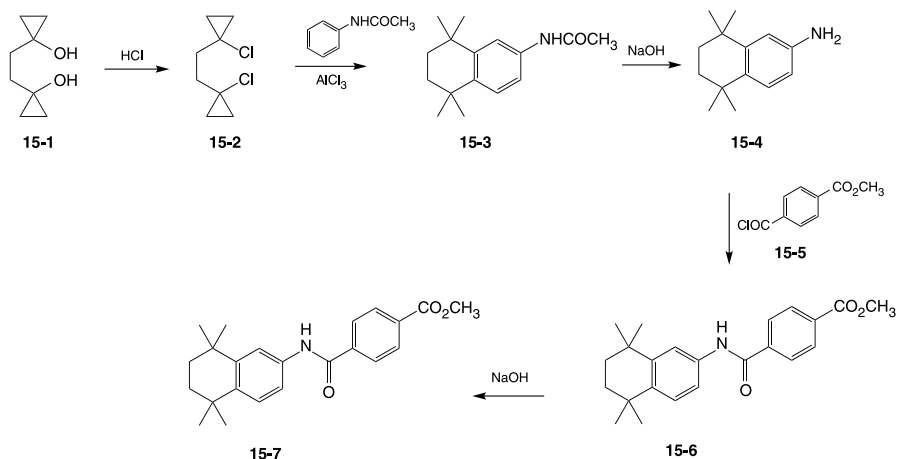
The retinoid-like compound **bexarotene** (**16-5**) is approved for treating skin lesions associated with T-cell lymphomas. The starting tetralin (**16-1**) is probably obtained by alkylation of toluene with dichloride (**15-2**). Friedel–Crafts acylation with the same acid chloride (**15-5**) as in the preceding example gives the ketone (**16-2**). This intermediate is then treated with the ylide from triphenylmethylphodphonium bromide. The carbonyl oxygen in the precusrsor (**16-2**) is now replaced by a methylene group (**16-3**). Saponfication of the ester affords the free acid and thus **bexarotene** (**16-4**) [18].
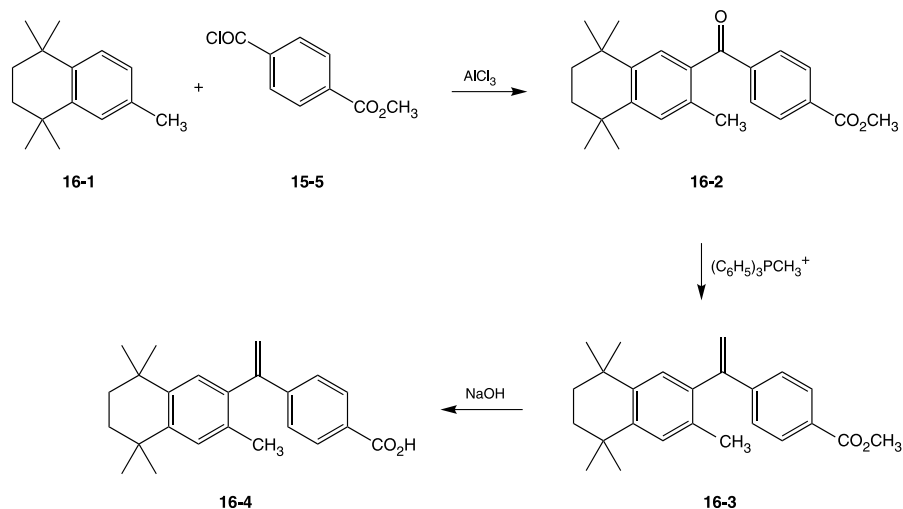
3.3.2. Another β-Blocker

A propanolamine chain comprises an almost invariant substituent in the multitude of β-adrenergic blocking agents. Modification on the aryl portion to which that pharmacophore is attached can serve to modify the pharmacodynamic properties of individual drugs. Partial agonist action is a common property exhibited by receptor antagonists in many pharmacological classes. Appropriate substitution can decrease the undesired intrinsic β-adrenergic agonist action shown by many β-blockers. Thus replacement of one of the rings in the naphthalene moiety in **propranolol** (**1-1**) by a partly reduced ring bearing a diol been shown to reduce β-adrenergic agonist activity.

The synthesis of that agent, **nadolol** (**17-7**), starts with Birch reduction of 1-naphthol (**17-1**). These dissolving metal reductions usually show selectivity for the ring bearing electron-rich substituents; a ring carrying a methoxy group will more often than not be reduced in preference to a ring that bears no substituents. In the case at hand, the phenol ring is protected against reduction by the fact that it bears a negative charge under the very basic reaction conditions. Treatment of (**17-1**) in liquid ammonia with lithium followed by ethanol as a proton source thus gives the dihydronaphthol (**17-2**). The phenolic group is then acetylated as protection from the oxidative reagents used in the next step. The required *cis* diol function is then introduced by means of iodine and silver acetate in the Woodward modification of the Prevost oxidation. The reaction can be rationalized by assuming the formation of the cyclic iodonium intermediate (**17-3**) as the first step. Attack by an acetate anion will lead to a *trans* iodoacetate such as (**17-4**) as well as its regio-isomer; each will lead to the same final product. Displacement of the reactive iodo group then leads to triacetate (**17-5**). This is not isolated but converted *in situ* with a strong base to triol (**17-6**). The oxypropanolamine side chain is then introduced in the usual way by sequential reactions with epichlorohydrin and *tertiary* butylamine. The halide reacts selectively at the phenol by reason of its far greater acidity than the aliphatic hydroxyl groups. There is thus obtained the β-blocker **nadolol** (**17-7**) [19].
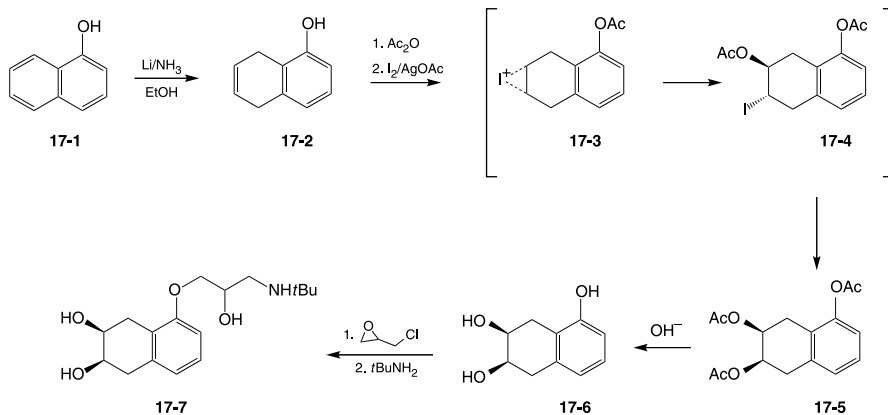
3.3.3. Aminotetralin CNS Agents

The shortcomings of the traditional tricyclic antidepressant drugs such as **amitriptyline** and its active metabolite **nortriptyline** (**18-1**), discussed later in this chapter, seemed not to be extensions of the drugs' pharmacologies. This encouraged the investigation of topological analogues, that is, compounds that have similar functionality supported on a different carbon skeleton. This offers the possibility for designing drugs that have the same activity but may be devoid of the side effects attributed to the structural class.
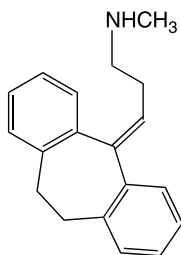
18-1

The structure of **nortriptyline** (**18-1**) depicted above in an admittedly biased projection suggested 4-aryl-1-aminotetralins as possible topological analogues by the formal opening of the seven-membered ring and then cyclizing the side chain. The preparation of the first of these agents starts with 4,4-diphenylbutyric acid (**19-1**).
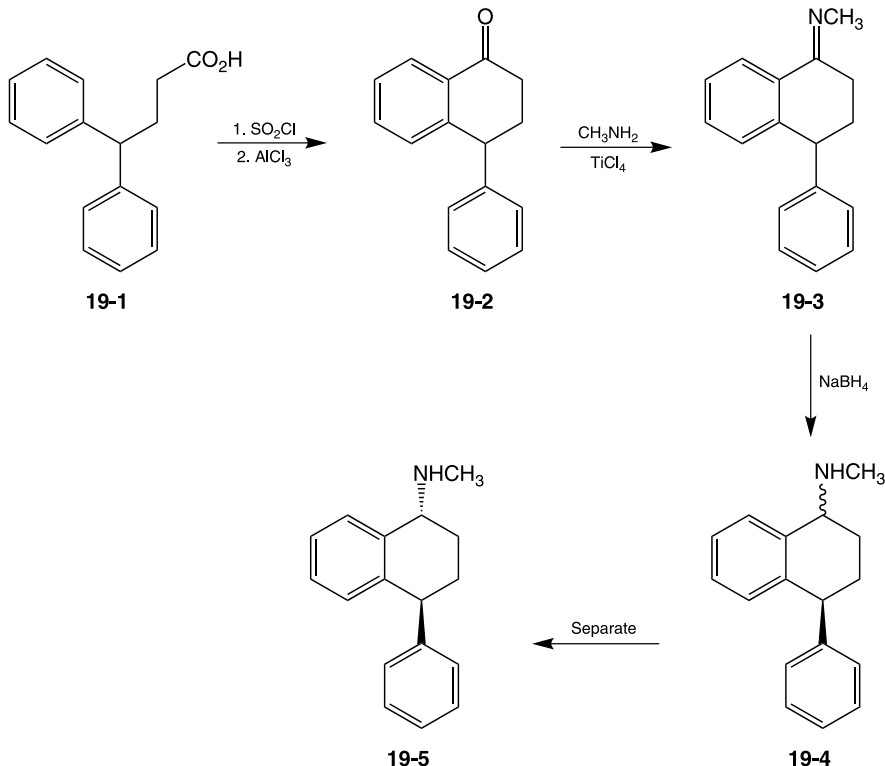
Cyclization of the acid chloride by means of aluminum chloride gives tetralone (**19-2**). This is then converted to its *N*-methylimine (**19-3**) by means of methylamine and titanium tetrachloride. That intermediate is next reduced with sodium borohydride to give a mixture of *cis* and *trans* aminotetralins (**19-4**). The *trans* isomer **tametraline** (**19-5**) is separated by fractional crystallization of the hydrochloride salt [20]. Detailed pharmacological investigations showed that this compound owes its antidepressant action to the inhibition of reuptake of dopamine and norepinephrine from the synaptic cleft.

A somewhat more elaborate scheme is used for the analogue bearing different substitution on the pendant phenyl ring. Stobbe condensation of substituted benzophenone (**20-1**), itself obtainable from Friedel–Crafts acylation of benzene with 3,4-dichlorobenzoyl chloride, with ethyl succinate and potassium *tertiary*-butoxide gives the chain extended half-ester (**20-2**). Treatment of that product with hydrobromic acid leads to the hydrolysis of the remaining ester group with concomitant decarboxylation to give the acrylic acid (**20-3**) as a mixture of isomers. The total product is then hydrogenated to the 4,4-diarylbutyric acid (**20-4**). Friedel–Crafts cyclization proceeds by attacking the more electron-rich of the two benzene rings to afford the tetralone. This last intermediate is then converted to its *N*-methylimine with methylamine in the presence of titanium tetrachloride (**20-5**). Hydride reduction leads, as above, to a mixture of *cis* and *trans* aminotetralins. The *cis* isomer, **sertraline** (**20-6**), is then separated by column chromatography [21]. This compound is also an antidepressant though, in contrast to the *trans* tetralin **tametraline**, it acts mainly by inhibiting the reuptake of serotonin.
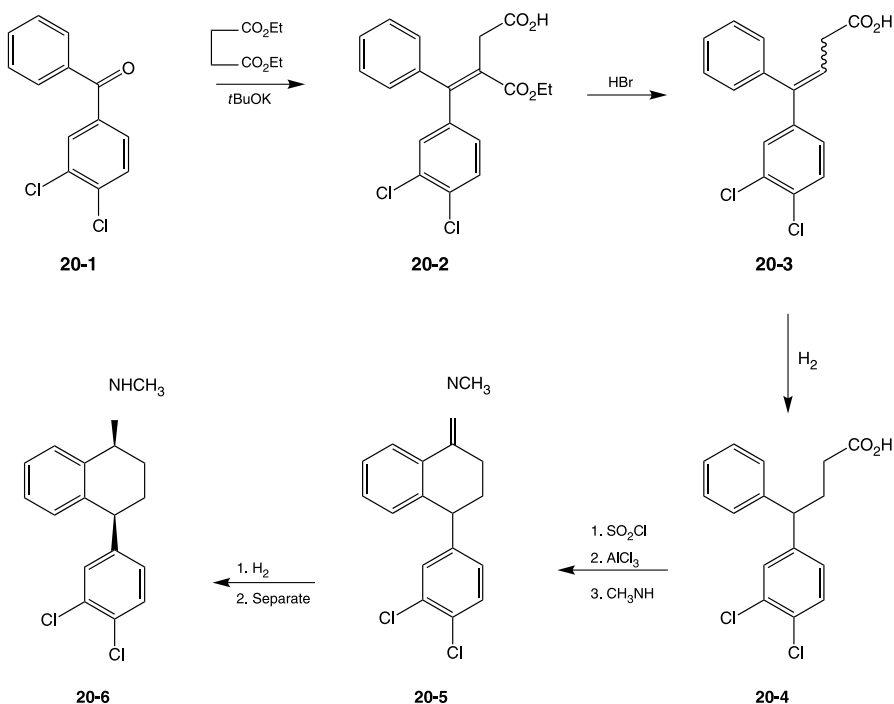
Yet another tetralin-based antidepressant differs from the preceding examples by omission of the pendant benzene at the position opposite to the amine. This agent not only inhibits the reuptake of norepinephrine but also exhibits potent α-2 adrenergic activity. The synthesis starts by converting the tetralone (**21-1**) to the silylated cyano-hydrin (**21-2**) by means of trimethylsilyl cyanide. Treatment of the crude product with a strong acid leads to the equivalent of dehydration to afford an unsaturated nitrile (**21-3**). Reaction of that intermediate with ammonia in the presence of Raney nickel reduces both the unsaturation and the nitrile to afford the primary amine (**21-4**). In a short converging sequence, 2-phenylsuccinic acid (**20-5**) is reduced to the corresponding diol with lithium aluminum hydride. That diol is then converted to the bidentate mesylate (**21-6**) with methansulfonyl chloride. Reaction of the primary amine (**21-4**) with that alkylating agent leads to the formation of a pyrrolidine and thus the antidepressant **napitane** (**21-7**) [22].
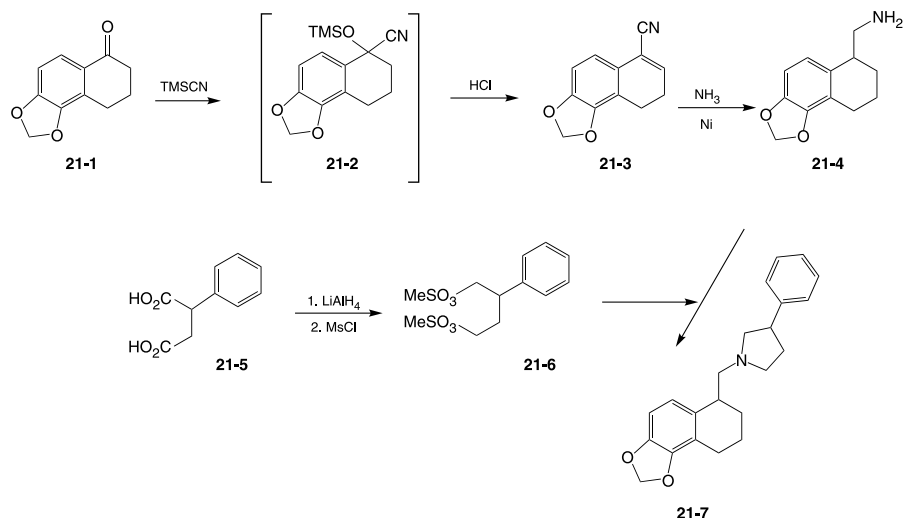
Drug therapy for treating Parkinson's disease involves supplementing the deficient levels of dopamine in the brain that characterize the disease. The blood−brain barrier virtually dictates that the agents need to be lipophillic; dopamine itself is too hydro-philic to penetrate the brain from the circulation. A tetrahydronaphthalene derivative that incorporates one of the phenolic hydroxyls as well as an ethylamine-like sequence of dopamine shows the same activity as the neurotransmitter. The lipophi-licity of **rotigotine** (**22-10**) allows it not only to cross the blood−brain barrier but to also reach the circulation when administered topically. The drug is in fact provided as a skin patch formulation that provides prolonged blood levels. The preparation of this dopaminergic agent starts with the conversion of the dihydroxynaphthalene (**22-1**) to its methyl ether (**22-2**) by means of dimethyl sulfate. Treatment of that with sodium in alcohol leads initially to the dihydro intermediate (**22-3**). The regiochemistry follows from the fact that only the right-hand ring has two open positions in a 1,4 relationship to the methyl ether for forming the initial metal adduct. Treatment of (**22-3**) with acid

then hydrolyzes the enol ether to afford the β-tetralone (**22-4**). The carbonyl group is next converted to imine (**22-5**) by reaction with propylamine. Catalytic hydrogenation of the intermediate then affords the secondary amine. This intermediate (**22-6**) is resolved via its dibenzoyl tartrate salt. The methyl ether in the S enantiomer is cleaved by means of hydrogen bromide to give the corresponding phenol (**22-7**). Reaction with an activated form of 2-thienylacetic acid (**22-8**) followed by reduction of the thus-obtained amide (**22-9**) with diborane gives the corresponding tertiary amine, **rotigotine** (**22-10**) [23].
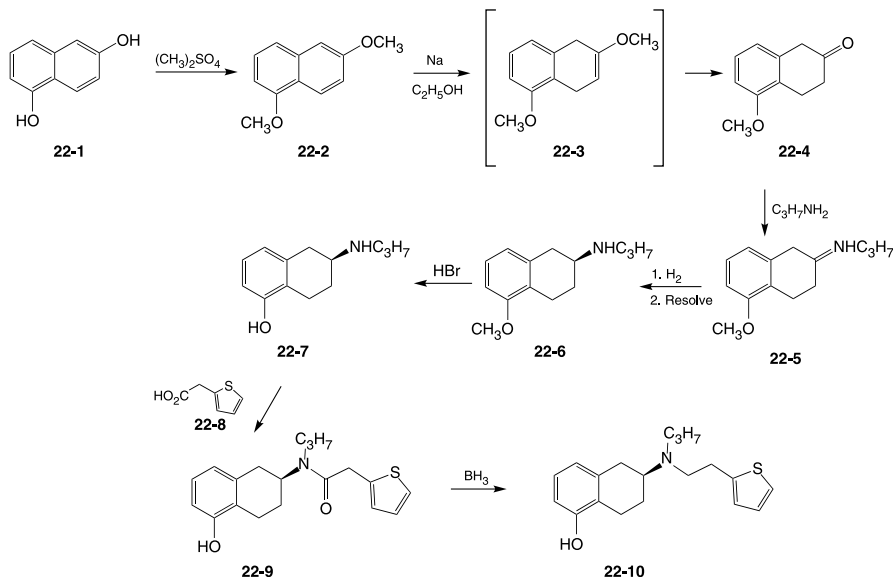
3.4. TRICYCLIC COMPOUNDS

3.4.1. Dibenzocycloheptane and Dibenzocycloheptene Antidepressants

The discovery of the antipsychotic activity of **chlorpromazine** (**23-1**) opened the modern era of psychopharmacology. An intense effort ensued in many laboratories to investigate the structure-activity relationships of related compounds. This included the preparation of what may be regarded, possibly *post facto*, as a carbo-cyclic bioisostere of a phenothiazine, with the sulfur bridge of the prototype being replaced by an ethylene chain of approximately the same size and the nitrogen bridge by a trigonal sp^2 carbon. The resulting compound, **amitriptyline** (**23-2**), unex-pectedly showed antidepressant rather than antipsychotic activity. It is now known that the antipsychotic effect of the phenothiazines is due mainly to the fact that they are competitive antagonists for dopamine at its receptor sites; the tricyclic antidepressants, on the other hand, inhibit the reuptake of norepinephrine and

serotonin from the synaptic cleft, in effect prolonging the action of those two neuro-transmitters.
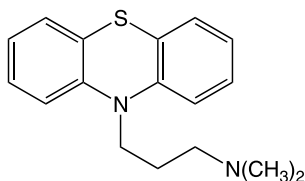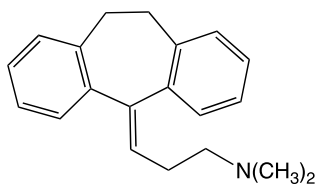
23-1   **23-2**

Preparation of the starting material for compounds in this series hinges on the fact that the protons on the methylene group in phtalide (**24-1**) are surprisingly acidic; this compound thus readily undergoes aldol condensation with benzaldehyde to give the benzal derivative (**24-2**) that is in effect an internal enol ester. Reaction with phosphorus and hydriodic acid serves to reduce the carbonyl group; there is thus obtained the stilbene carboxylic acid (**24-3**). Catalytic hydrogenation of the double bond leads to (**24-4**); this compound can then be cyclized to dibenzocycloheptanone (**24-5**) under standard Friedel–Crafts conditions as, for example, treatment with polyphosphoric acid (PPA). Cyclization of the corresponding unsaturated acid (**24-3**) leads to the ketone (**24-6**); this last product can be reduced to the corresponding hydrocarbon (**24-7**) by Wolff-Kishner reduction with hydrazine and potassium hydroxide.
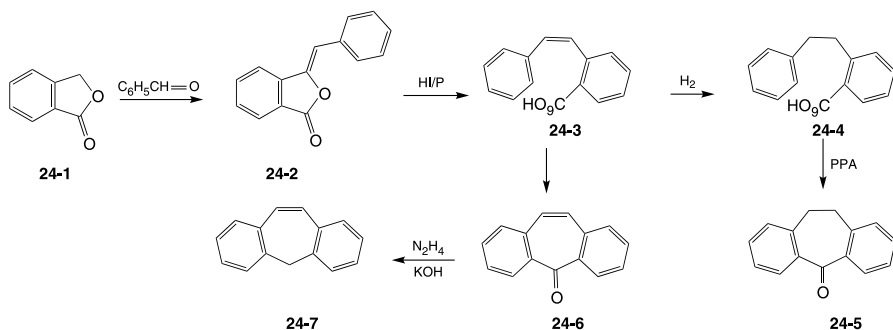
One of the more direct syntheses of the prototype compounds in this series, **amitriptyline** (**23-2**), depends on the cyclopropylcarbinyl-homoallyl rearrangement derived from steroid chemistry and discussed in greater detail in Chapter 1. The key intermediate (**25-1**) is obtained by condensation of the Grignard reagent from cyclopropyl chloride with dibenzocycloheptanone (**24-5**). Reaction of the product with hydrogen bromide leads to the rearrangement of the cyclopropyl carbinol to the homoallyl bromide (**25-2**) via an intermediate homoallyl carbocation. The displacement of halogen with dimethylamine affords **amitriptyline** (**23-2**); the corresponding reaction with methylamine affords **nortiptyline** (**25-3**) [24].

The more conventional approach used for the synthesis of the analogue incorporating a branched side chain involves additional steps, which are not shown but are required for

preparing the starting material for that chain. Once the required *N,N*-dimethyl-3-chloro-2-methylpropylamine is at hand, it is converted to its corresponding Grignard reagent. Condensation with dibenzocycloheptanone affords the amino alcohol (**25-4**). Dehydration by treatment with a strong acid affords **butriptyline** (**25-5**) [25].
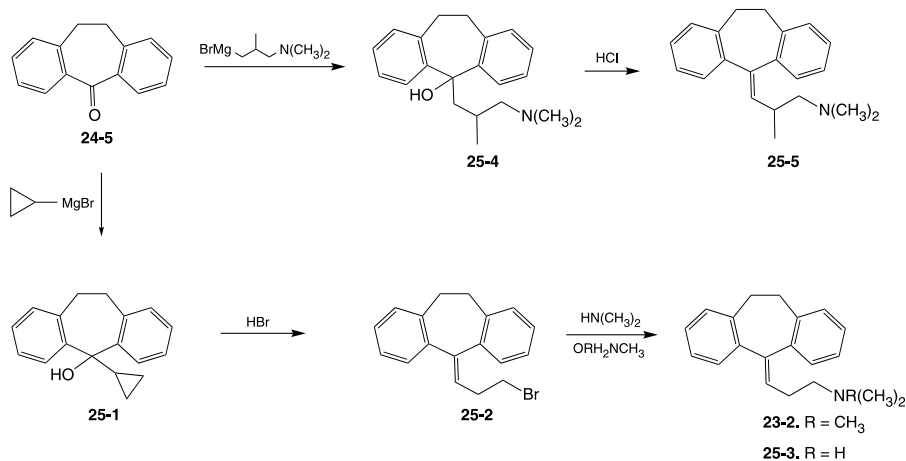
An analogue in which the side chain is cyclized to form a piperidine ring, **cyproheptadine** (**26-2**), interestingly shows predominantly the antihistaminic activity that led to the preparation of the phenothiazines in the first place. This analogue is prepared in a straightforward fashion by condensation of the Grignard reagent from chloropiperidine (**26-1**) with (**24-6**); dehydration of the intermediate alcohol gives **cyproheptadine** (**26-2**) [26].
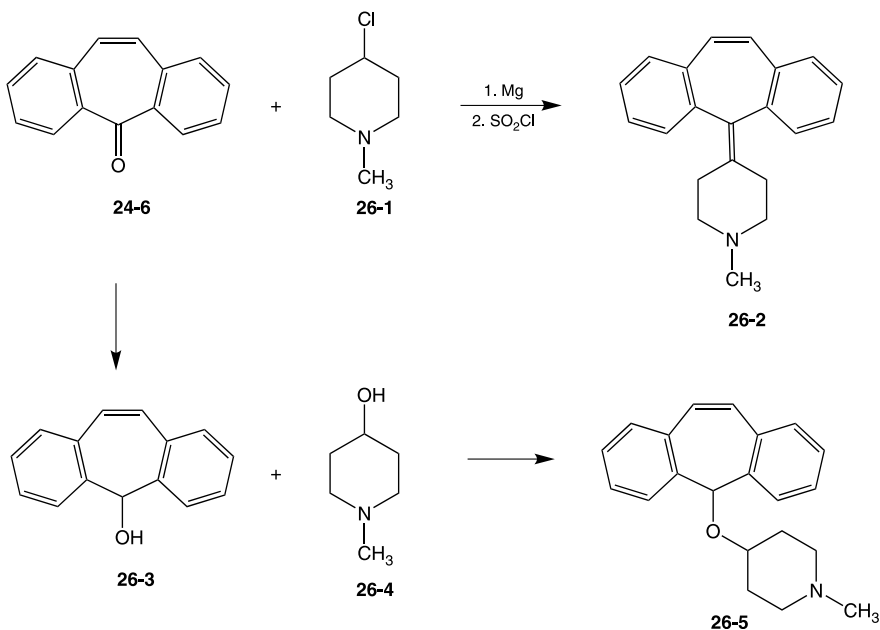
Extension of the side chain by the interposition of ether oxygen restores the antidepressant activity even when nitrogen is included in a piperidine ring; it is not clear whether the unsaturation in the cycloheptene ring plays a role in this. The starting alcohol (**26-3**) is obtained by hydride reduction of dibenzocycloheptenone (**24-6**). Reaction of the product with a strong acid in the presence of *N*-methyl-4-piperidinol in all likelihood proceeds to first form dibenzyl carbocation by the loss of water from protonated (**24-6**); reaction with oxygen on piperidinol will then give the observed product, **hepzidine** (**26-5**) [27].

Dibenzocycloheptenone (**24-6**) also serves as a starting material for the preparation of one of the few medicinal products that contains an acetylenic linkage. Reaction of (**24-6**) with the Grignard reagent from propargyl bromide leads to the alcohol (**27-1**). The free proton acetylene is sufficiently acidic for that center to take part in a Mannich reaction. Thus, reaction of (**27-1**) with formaldehyde and dimethylamine gives the adduct (**27-2**). Dehydration by means of thionyl chloride completes the synthesis of **intriptyline** (**27-3**) [28].
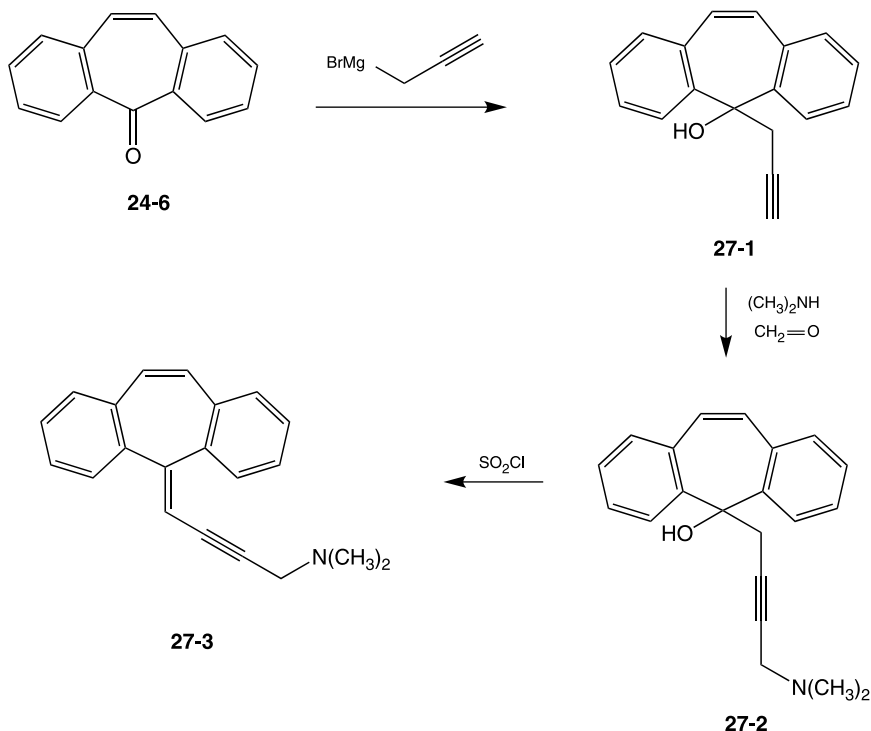
Antidepressant activity is retained when the double bond in the cycloheptene ring is replaced by a fused cyclopropane. The starting material for this compound is obtained by the reaction of unsaturated ketone (**24-6**) with dichlorocarbene

formed by the reaction of ethyl trichlororacetate acid with a strong base to give the cyclopropylated product (**28-1**). In a sequence patterned after that used for the proto-type drug, the product is next condensed with the Grignard reagent from cyclopropyl chloride to give carbinol (**28-2**). The halogen is then removed by dissolving metal reduction with lithium and *tertiary*-butanol to give (**28-3**). This intermediate is then subjected to the cyclopropylcarbinyl rearrangement to give a homoallyl halide (**28-4**); this step also does away with any potential problems posed by geometrical isomerism. The displacement of halogen with dimethylamine affords the antidepress-ant agent **octriptyline** (**28-5**) [29].

24-6   **28-1**   **28-2**

28-5   **28-4**   **28-3**
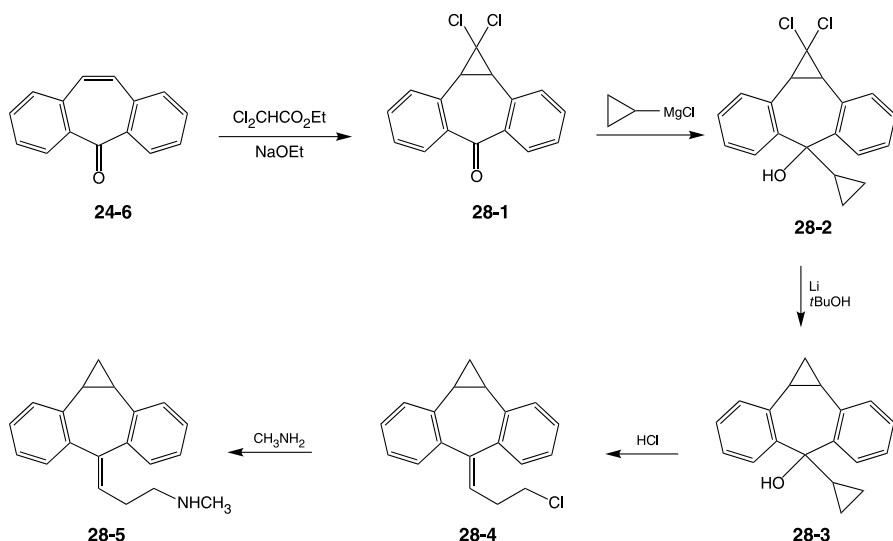
Compounds in this dibenzocycloheptene series also manifest antidepressant activity when the trigonal one-carbon bridge is replaced by tetrahedral carbon. Thus, the reaction of hydrocarbon (**24-7**) with a metal amide in liquid ammonia leads to the corresponding carbanion (**29-1**). Treatment of that with the ethyl carbamate from *N*-methyl-3-chloropropylamine (**29-2**) leads to the alkylation product. The carbamate protecting group is then removed by sequential saponification with a base followed by acidification. This yields the antidepressant agent **protripty-line** (**29-3**) [30].

24-7   **29-1**   **29-3**
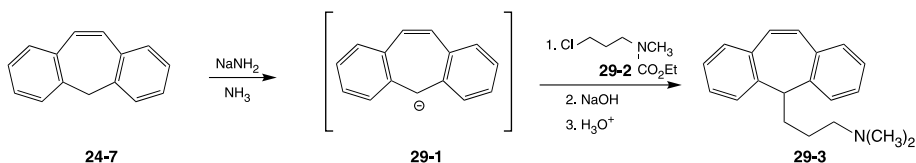
3.4.2. Antidepressants Based on Dihydroanthracenes

The contraction of the central ring in the classical tricyclic agents to a dihydroanthracene is compatible with antidepressant activity though the resulting compounds at first sight more closely resemble the antipsychotic phenothiazines. Most of this small group of drugs owe their antidepressant activities to the inhibition of the reuptake of norepinephrine.

The synthesis of the simplest member of this series, **melitracen** (**30-3**), takes advantage of the relatively acidic protons of the methylene group in anthrone (**30-1**) due to activation from the carbonyl group transmitted via the aromatic rings. Thus treatment of the carbanion from anthrone with methyl iodide proceeds to the dimethyl derivative (**30-2**). The Grignard reagent from *N,N*-dimethyl-3-propylamine is then added to the carbonyl group of that intermediate. Dehydration of the resulting carbinol gives **melitracen** (**30-3**) [31].
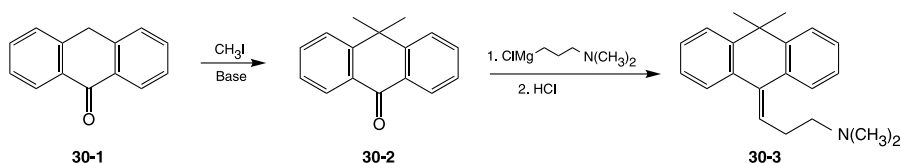
A rather more complex scheme is required for the preparation of a derivative that bears a trifluoromethyl substituent on one of the benzene rings. The scheme starts with the condensation of the nitrile group in (**32-1**) with phenylmagnesium bromide to give the corresponding imine; treatment with aqueous acid leads to the substituted benzophenone (**32-2**). The future methyl on one of the bridges is introduced in a sequence involving the addition of a trimethylsulfonium ylide.
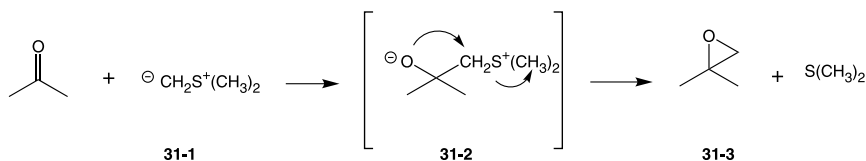
The first step in that reaction involves the straightforward addition of the anion to the carbonyl group to give a betaine such as (**31-2**). Internal displacement of dimethyl sulfide by the newly formed alkoxide anion leads to an epoxide and, when starting with the benzophenone (**32-1**), intermediate (**32-3**). Reaction with red phosphorus and hydriodic acid leads to a fully reduced methyl derivative. This reduction may be rationalized by assuming an initial opening to an iodohydrin followed by the subsequent reductive elimination of the benzhydrol hydroxyl and aliphatic iodine. The resulting intermediate (**32-4**) is then reacted with cuprous cyanide; this leads to the displacement of bromine by cyanide and the formation of nitrile (**32-5**). This is then condensed with the Grignard reagent from 3-bromo-1-methoxypropane to give

the imine (**32-6**). Treatment with hydrobromic acid leads directly to an anthracene (aromatization presumably results from bond reorganization of the presumed first-formed intermediate, which would contain an *exo* double). The reaction conditions are sufficiently strenuous to at the same time cleave the terminal methyl ether and to then convert the thus-formed alcohol to a bromide. Construction of the side chain is completed by the replacement of halogen by dimethylamine (**32-7**). Catalytic reduction proceeds to give the 9,10-*cis*-dihydroanthracene and thus **fluotracen** (**32-8**) [32].
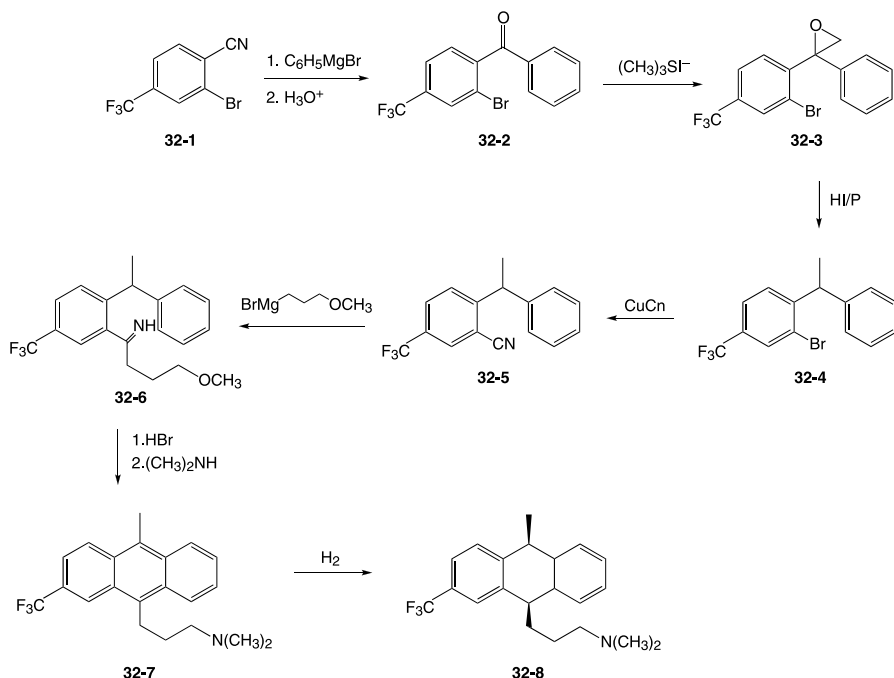
The first step in the preparation of the antidepressant **maprotiline** (**33-5**) takes advantage of the acidity of anthrone protons for incorporation of the side chain. Thus treatment of (**30-1**) with ethyl acrylate and a relatively mild base leads to the Michael adduct; saponification of the ester group gives the corresponding acid (**33-1**). The ketone group is then reduced by means of zinc and ammonium hydroxide. Dehydration of the first-formed alcohol under acidic conditions leads to the formation of fully aromatic anthracene (**33-2**). Diels–Alder addition of ethylene under high pressure leads to the addition across the 9,10 positions and the formation of the central 2,2,2-bicyclooctyl moiety (**33-3**). The final steps involve the construction of the typical antidepressant side chain. The acid in (**33-3**) is thus converted to an acid chloride and that function reacted with methylamine to form the amide (**33-4**). Reduction to a secondary amine completes the synthesis of (**33-5**) [33].
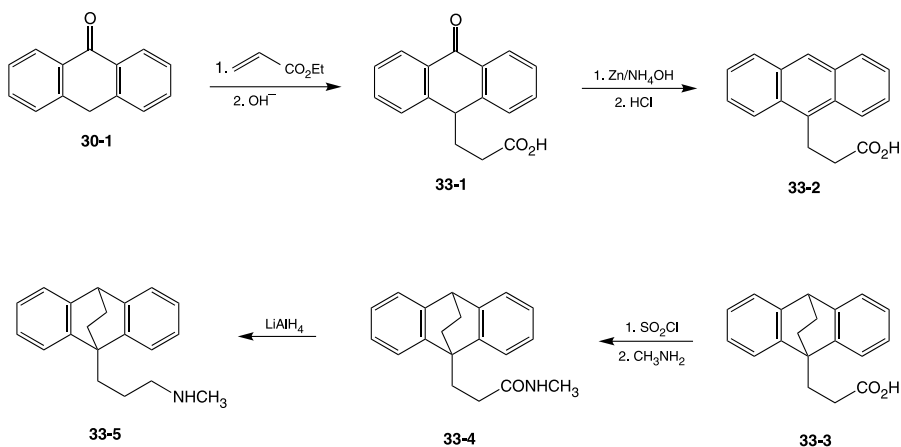
The aminoalcohol side chain in the antidepressant **oxaprotiline** (**34-5**) interestingly resembles that of a β-blocker, though no such activity has been reported for the compound. The first few steps in the synthesis leading to the key intermediate (**34-1**) parallel those for **maprotiline** (**33-1–33-3**) starting with an acetic rather than a propionic acid. The carboxyl group is then reduced to an aldehyde by sequential conversion to its acid chloride and then hydrogenation over a poisoned palladium catalyst. Reaction of the aldehyde (**34-2**) with hydrogen cyanide leads to the corresponding cyanohydrin (**34-3**), which now incorporates the required third side chain carbon. Reduction with lithium aluminum hydride yields the aminoalcohol (**34-4**) [34]. The primary amino group can then be monomethylated by any of several methods such as conversion to its carbamate followed by a second hydride reduction.
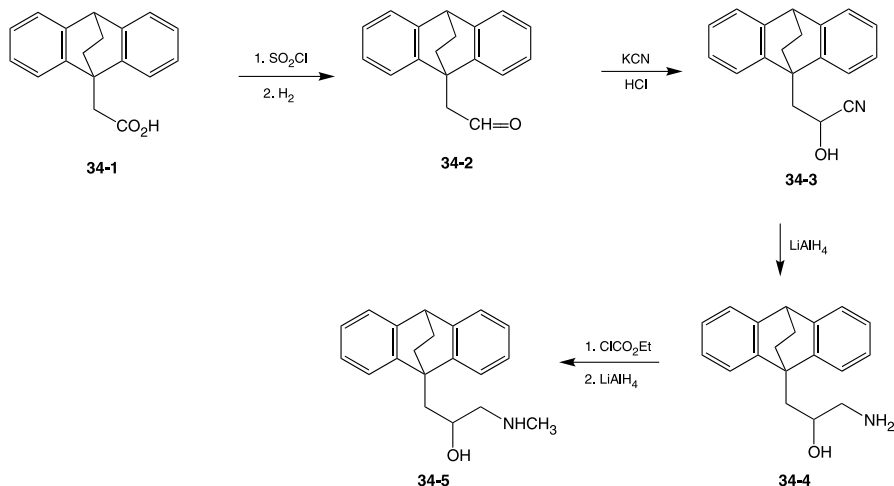
3.4.3. Anthraquinones: The "Antrone" Chemotherapy Agents

Anthraquinones have a venerable history as dyes that traces back to the late nineteenth century. Their use as drugs is much more recent, dating from the early 1980s. The initial discovery of the activity of this class was due to the lack of any good leads for compounds that were useful for the treatment of cancer. This led the National Cancer Institute (NCI) of the U. S. National Institutes of Health to undertake a massive screening program for compounds that might show antineoplastic activities. In pursuit of that program, the NCI and its representatives scoured all possible sources worldwide for compounds for submission to the screens. In order to acquire the broadest possible selection of structural types, potential sources included a large number of chemical and pharmaceutical concerns as well as laboratories in academia. A dark blue anthraquinone originally developed as a ball point ink pigment perhaps unexpectedly showed activity in the mouse leukemia screen then used by the NCI. Though this compound, **ametantrone** (**35-4**), never reached the clinic, its more hydrophilic congener, **mitoxantrone** (**36-3**), was eventually approved for the treatment of leukemia.
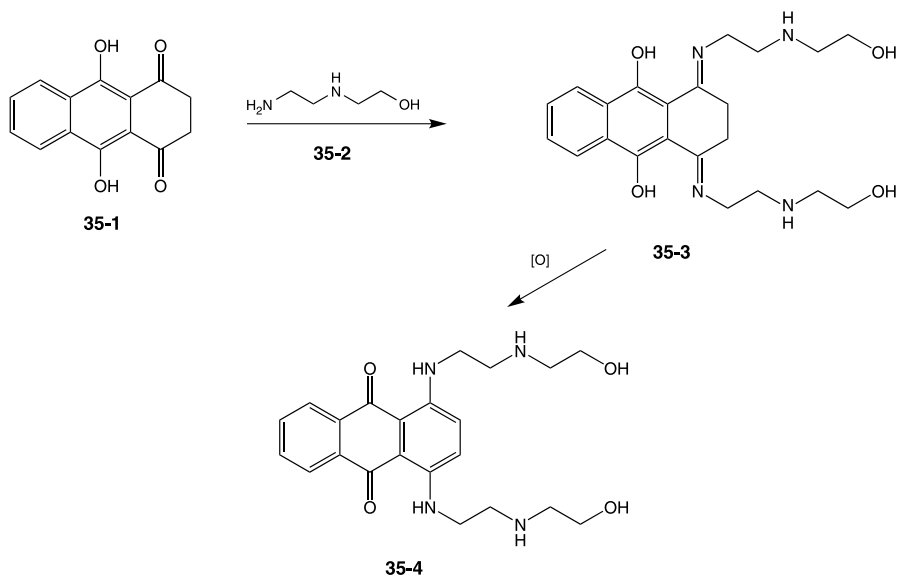
The synthesis of the first of these agents starts with the dye intermediate leucoquinizarin (**35-1**), the reduction product of the dihydroxyanthraquinone, quinizarin. Condensation with *N*-(2-hydroxyethyl)ethylenediamine (**35-2**) leads to the corresponding *bis* imine (**35-3**). Air oxidation may be visualized as starting at the hydroquinone-like central ring; bond reorganization will lead to **ametrantrone** (**35-4**) [35].

In much the same vein, condensation of the tetrahydroxy intermediate (**36-1**) with the same polyamine as above gives the analogous intermediate *bis* imine; air oxidation of the intermediate then affords **mitoxantrone** (**36-2**) [36].

36-1   **35-2**   **36-2**
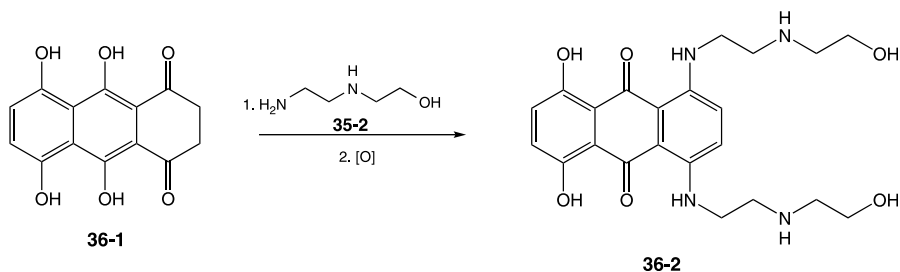
Good activity is retained in these compounds when one of the quinone oxygens is included in a pyrazole ring. The preparation of one of these agents, **piroxantrone** (**37-6**), starts by protection of the hydroxyl groups in 1,4-dichloro-5,8-dihydroxy-anthraquinone as their benzyl ethers to give (**37-1**). Condensation of that with the hydrazine counterpart (**37-2**) of the reagent used to prepare the preceding examples leads to the pyrazole intermediate (**37-3**); the order in which the steps involved in forming the heterocyclic ring, imine formation, and nucleophilic displacement of aromatic chlorine occur is not immediately apparent. The remaining aromatic halogen is then displaced with 1,3-propylene diamine (**37-4**) to give (**37-5**). Removal of the benzyl ethers by hydrogenolysis completes the synthesis of **piroxantrone** (**37-6**) [37,38].

37-1   **37-2**   **37-3**   **37-4**   **37-5**   **37-6**
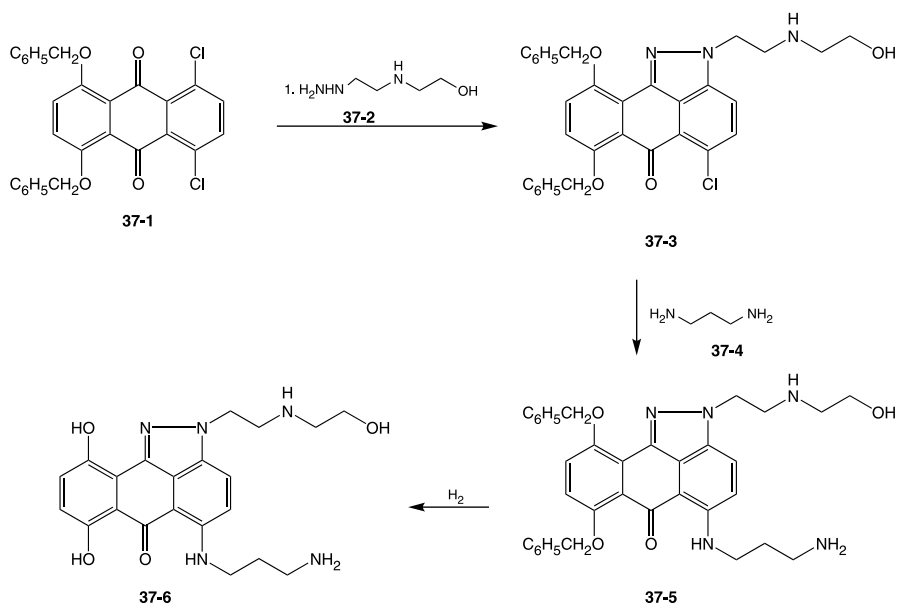
The symmetrical substitution pattern in the foregoing starting anthraquinones greatly simplified the chemistry. The presence of but a single hydroxyl substituent

on the terminal ring of the pyrazolo derivative **losoxantrone** (**38-5**) adds to the complication of its preparation. The phenol in the key intermediate in this case is protected as its somewhat more bulky 2,4,6-trimethylbenzyl intermediate (**38-1**). The additional methyl groups may help steer the condensation away from the adjacent carbonyl group and in addition add lipophilicity, which aids in the solubility of intermediates in common organic reaction solvents. Condensation with the same hydrazine as above leads to a mixture of (**38-2**) and its isomer as a 4 : 1 mixture. The crude mixture is then converted to its *t*-BOC derivative in order to facilitate separation. Treatment of the purified derivatized intermediate with trifluoroacetic acid removes the *t*-BOC and benzyl groups in a single step to give (**38-2**). Displacement of the remaining chlorine by means of the by-now familiar *N*-(2-hydroxyethyl)ethylenediamine then gives **losoxantrone** [37,38].
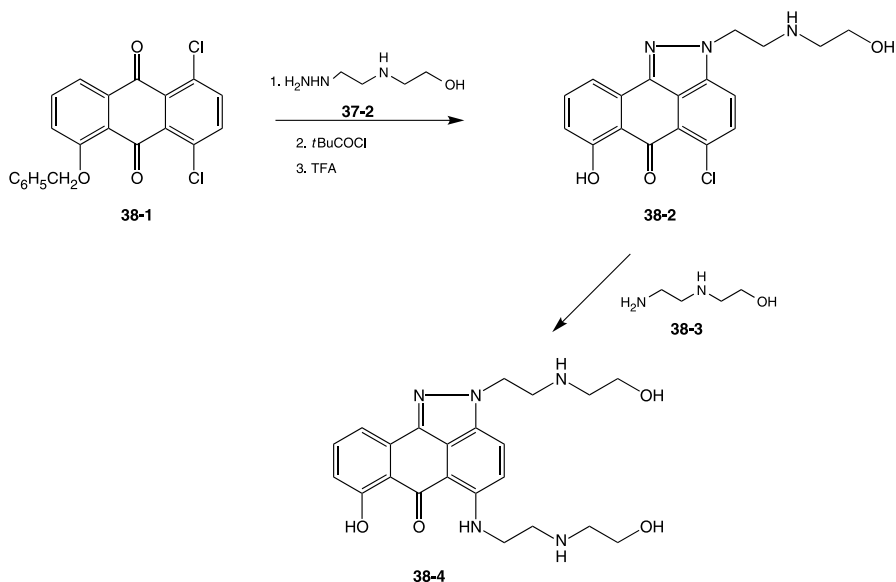
An earlier congener, **bisantrene** (**39-8**), shares the linear tricyclic ring system and a wealth of nitrogen atoms with the antrones. The unusual method used for adding functionals that anchor the side chains at the bridgehead positions hinges on the diene-like character of the central ring in anthracene. Thus, Diels–Alder condensation of anthracene (**39-1**) with vinylene carbonate (**39-2**) leads to the key intermediate, adduct (**39-3**). Hydrolysis with a mild acid removes the carbonate group and affords the diol (**39-4**). Cleavage by means of periodic acid leads to the 1,9-dialdehyde (**39-5**). Oxidation then serves to aromatize the central ring (**39-6**). The carbonyl groups are then converted to the corresponding hydrazones by reaction with 2-hydrazinoimidazoline (**39-7**). There is thus obtained the chemotherapy agent **bisantrene** (**39-8**) [39].
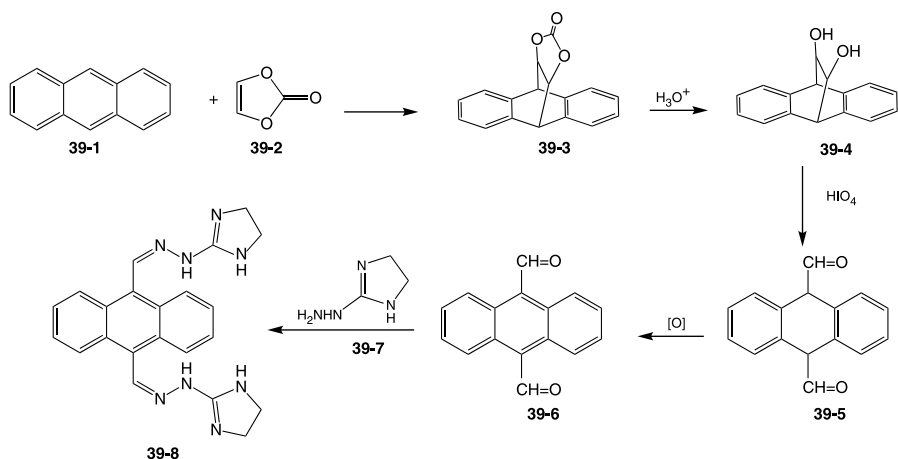
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CHAPTER 4

STEROIDS; PART 1: ESTRANES, GONANES, AND ANDROSTANES

4.1. INTRODUCTION

The fused tetracyclic steroid nucleus provides the carbon framework for at least five large groups of mammalian hormones; these comprise the estrogens, androgens, progestins, and corticosteroids and the compounds that comprise the D vitamins. The parent molecule, cholesterol, in addition, plays an important structural role in many membranes. That nucleus is interestingly ubiquitous in nature and occurs in both plant and animal species. The fact that it is a product of one of the isoprene pathways may in part explain this widespread distribution. The pathway for the formation of cholesterol has been shown to closely follow the initial steps leading to the formation of all naturally occurring pentacyclic C_{30} triterpenes; the key common intermediate, squalene, is formed by head-to-head coupling of two activated C_{15} farnesol derivatives (arrow). Cyclization of this polyene, which has been shown to proceed via an epoxide at the 2,3 terminal olefin, leads to an intermediate that contains the *cyclo*-pentaperhydrophenanthrene nucleus. Two successive methyl group migrations then give the intermediate lanosterol, which has been isolated. (This compound abounds in the fat from sheep wool.) A series of catabolic enzymes then remove the remaining three superfluous methyl groups. The product, cholesterol, serves as the metabolic starting material for the endogenous synthesis of all other steroids.

The bulk of the work on structure determination of steroids long predated the availability of any of the modern instrumental methods. The structures of the compounds were worked out entirely by classical noninstrumental methods that relied

largely on degradation reactions to known simpler compounds, Rast molecular weight determinations, and elemental analyses. Elegant chemical reasoning played an enormous role in this very difficult work[*]. The somewhat idiosyncratic numbering system used in steroid chemistry is traceable to the fact that it was devised before the structure of the nucleus was fully established.

Squalene   Lanosterol   Cholesterol

Steroid Numbering   Normal Steroid Configuration
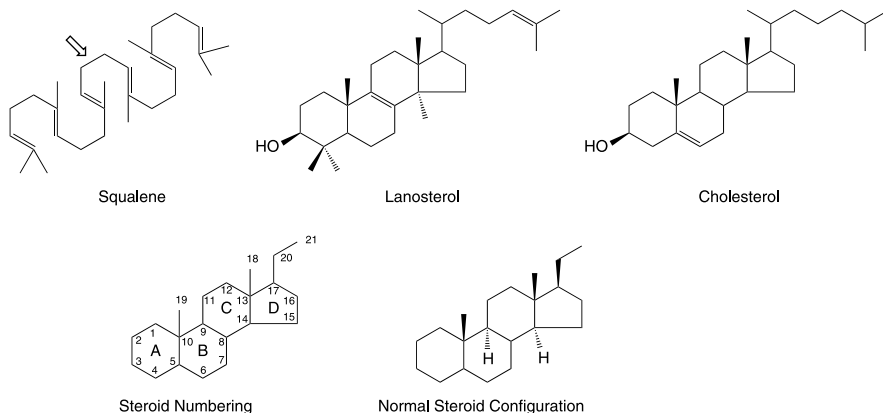
All naturally occurring steroids, and the overwhelming majority of those used as drugs, comprise single enantiomers. When written as in the flow schemes that follow, the diagrams depict the absolute configuration. Substituents below the plane of these rather flat molecules are named α while those above that face are named β, a convention that later spread to many other structural classes.

4.2. STEROID STARTING MATERIALS

The initial pharmacologic and clinical investigations on steroid hormones relied on supplies of those compounds isolated from mammalian sources. The difficult isolations involved in obtaining those supplies combined with the drive to prepare chemically modified entities led to the search for more abundant and easily accessible steroid starting materials among plant sterols. The structural and stereochemical complexities of these compounds largely rule out total synthesis as the means for preparing commercial quantities. The elegant syntheses that have been published for all steroid hormones are not usually competitive with semi-synthesis from natural products. Selected estranes and gonanes form an exception to that rule, as some of these compounds are more conveniently prepared by total synthesis. This is of necessity the case with those agents that include modifications not accessible from plant sterol-derived intermediates.

One commercially important class of steroid drugs, it should be noted, is still, interestingly, obtained by isolation from mammalian sources. The best-known drug

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[*]For a brief account of that work, see Lednicer, D., *New Drug Discovery and Development*, Wiley, Hoboken, NJ, 2007, pp. 111–113.

in this category, Premarin®, consists of conjugated estrogens that comprise a mixture of 3-sulfate esters of estrone, estradiol, and a host of related compounds. The product was until recently widely used as a post-menopausal estrogen supplement.

4.2.1. From Diosgenin

The glycoside dioscin from the Mexican wild yam root, *Dioscorea*, constituted the first plant source for steroid drugs. Hydrolysis of this saponin leads to the scission of the trisaccharide at the 3 position and the formation of the aglycone, diosgenin (**2-1**). Treatment of this acetal with hot acetic anhydride in the presence of *p*-toluene-sulfonic acid leads initially to the protonation of one of the acetal oxygens; that then eliminates to form an enol ether. The free hydroxyl groups are acetylated under reaction conditions to give diacetate (**2-2**) as the product. Oxidation by means of chromium trioxide leads to a preferential attack at the electron-rich enol ether double bond and formation of (**2-3**). This transformation in effect converts the extended side chain at C-17 in diosgenin to the acetyl group required for many steroid drugs. Heating that intermediate in acetic anhydride leads to elimination of the ester grouping β to the ketone; there is thus obtained 16-dehydropregnenolone acetate (**2-4**) [1]. As will be subsequently noted, the presence of the olefin at 17 allows ready entry to C-19 androstanes and provides the necessary function for the synthesis of potent 16 and 16,17 substituted corticosteroids.
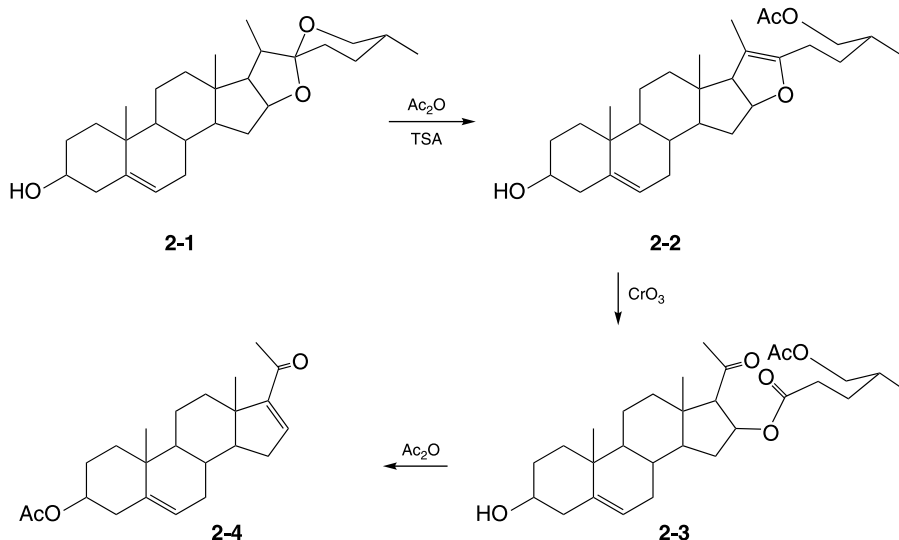
4.2.2. From Soybean Sterols

The chemistry for providing steroid raw materials from the far more readily available soybean sterols was developed somewhat later. The so-called unsaponifiable fraction

of soybean oil consists largely of stigmasterol (**3-1**) and sitosterol (**4-1**). The original process took advantage of the olefin in the side chain of the former for degrading that chain to an acetyl group. The first step involved the extraction of stigmasterol from the mixture by an ingenious leaching process. The 3-hydroxy-5-ene functionality is then converted to a conjugated enone in order to reduce its reactivity in subsequent steps. Thus, Oppenauer oxidation (cyclohexanone, aluminum isopropoxide) of (**3-1**) leads to the enone (**3-2**). Ozonization of that compound, followed by an oxidative workup of the ozonide, leads to aldehyde (**3-3**) in which the bulk of the side chain has been removed. The extraneous carbon atom is then removed by way of its eneamine (**3-4**), obtained by reaction of 7 with piperidine; photo-oxygenation of that intermediate leads directly to progesterone (**3-5**) [2,3].
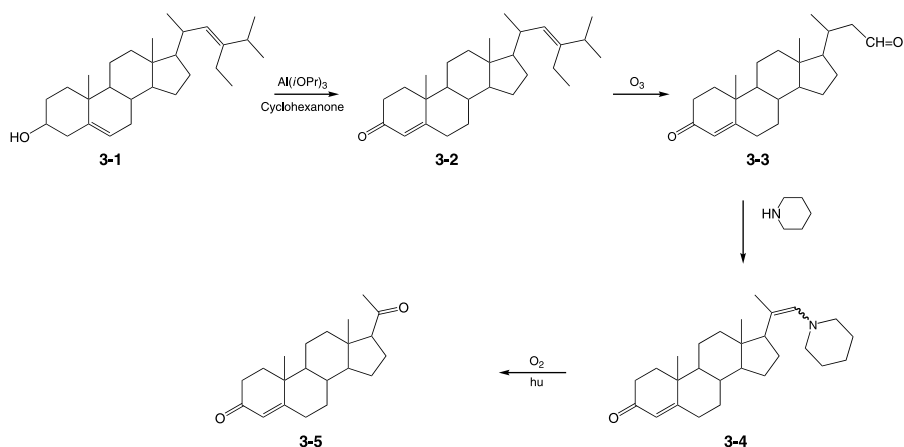
The byproduct sitosterol was for many years quite useless due to the lack of a chemical point of attack on the side chain that would permit its removal. Extensive efforts on the part of many laboratories eventually led to the discovery of a *pseudomonas* microbe that efficiently effected that transformation. Fermentation of (**4-1**) digests the entire aliphatic side chain at 17 to afford a mixture of 17-keto products including dehydroepiandrosterone (**4-2**) [4].
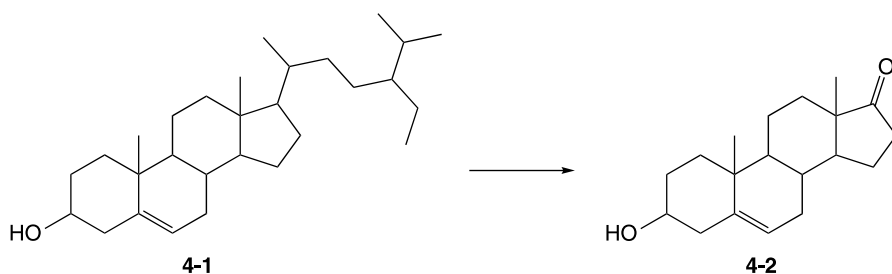
4.3. ESTRANES

4.3.1. Synthesis of Estranes

The estranes comprise the simplest steroids in terms of structure since the aromatic A ring removes two chiral centers. The endogenous compounds, estrone (**6-2**) and the corresponding alcohol, estradiol (**6-3**), play a central role in female reproductive endocrinology. Medical uses of pure estrogens or their derivatives are largely restricted to replacement therapy in those cases where endogenous levels are deficient. The use of conjugated estrogens to relieve post-menopausal symptoms has already been alluded to. Estranes are, however, used extensively as one of the components in oral contraceptives as well as starting materials for the so-called 19-nor steroids (gonanes).

The synthesis of estranes perforce invokes the need to perform an aromatization step that involves the unlikely expulsion of a methyl group due to the lack of natural products that have aromatic A rings in usable quantities. The starting dehydroepiandrosterone (**5-1**) may be obtained from fermentation as above or by degradation of 16-dehydropregnenolone [5]. Oxidation of that starting material under Oppenauer conditions gives androstene-3,17-dione (**5-2**). Catalytic reduction of the enone proceeds from the unhindered side to give the 5α dihydro derivative; this is then allowed to react with bromine in acetic acid. It has been shown that production of the observed 2α,4α dibromo derivative (**5-3**) in fact involves a complex series of intermediate reactions. Dehydrohalogenation of the product with 2,4,6-collidine leads to the 1,4-dieneone (**5-4**). This can be aromatized directly to estrone (**6-2**), albeit in very poor yield, by pyrolysis in mineral oil at 600°C [6]. A more practical method essentially involves the elimination of the quaternary methyl group as methyl lithium. The first step in the sequence thus consists of protecting the ketone at 17 as its propylene acetal (**5-5**). This is then heated with lithium metal in tetrahydrofuran (THF); the diphenymethane present in the reaction mixture presumably quenches the methyl lithium to prevent its adding to the starting dienone. There is thus obtained the estrone derivative (**5-6**) [6].
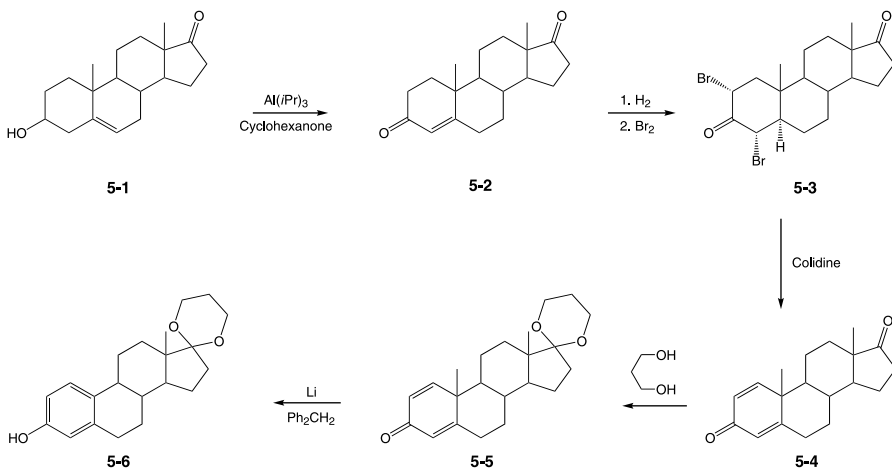
Hydrolysis of the acetal group then gives estrone (**6-2**). The 17 ketone can be reduced by any of several methods, such as borohydride, to give the 17β alcohol **estradiol** (**6-3**).
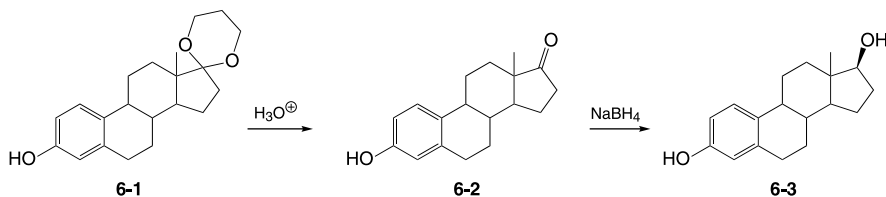
The so-called Torgov–Smith synthesis [7,8] provides a commercially practical route for the synthesis of estranes, particularly when combined with the resolution of the early intermediates. This approach is in fact mandatory for the synthesis of **norgestrel** (**17-4**), a gonane that bears an ethyl rather than a methyl group at the 13 position. The synthesis starts by the addition of the Grignard reagent from vinyl chloride to tetralone (**7-1**). The key step involves condensation of the allylic alcohol product (**7-2**) with cyclopentadione (**7-3**) in the presence of a catalytic amount of base. It is likely that this step, which gives the appearance of a simple displacement, in fact depends on the initial formation of an ambident allyl carbocation from (**7-2**) catalyzed by the quite acidic dione; addition of the enolate from the latter will give the observed product (**7-4**). This last intermediate is then treated with toluenesulfonic acid; cyclization leads to the tetracyclic intermediate (**7-5**). The structure of the steroids is notable for the fact that the CD ring fusion involves a thermodynamically disfavored *cis* hydrindane. The next step in the synthesis fortuitously establishes that stereochemistry; catalytic hydrogenation selectively reduces the 14,15 olefin; the addition of hydrogen from the more open α side of the molecule establishes the CD *trans* ring fusion. The ketone at the 17 position is then reduced to an alcohol with sodium borohydride. The remaining styrenoid olefin at the 9,10 positions is then removed by Birch reduction; it is likely that the stereochemistry of this reaction is determined by thermodynamics. There is thus obtained the 3-methyl ether of estradiol (**7-8**).
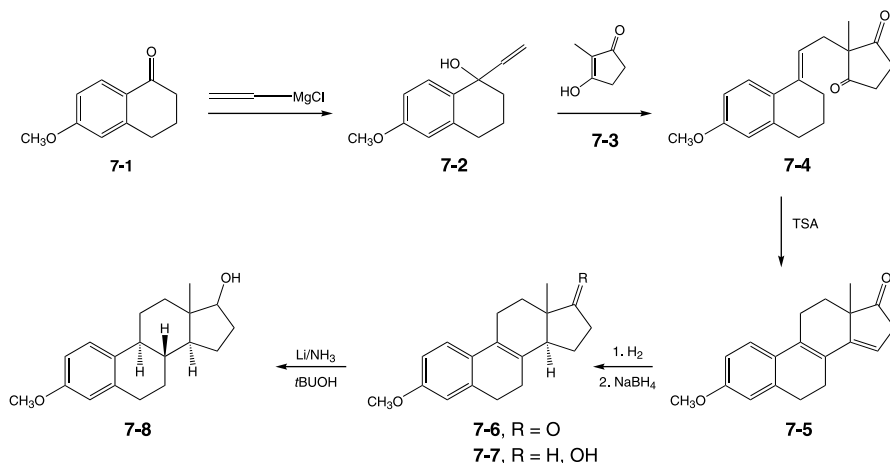
4.3.2. Drugs Based on Estranes

The finding that estrogens improved the endocrine status of post-menopausal women offered a much larger market for these compounds beyond simple replacement therapy. This indication has, however, been surrounded for the several past decades by controversy due to the conflicting risk–benefit ratios revealed by rival studies. This market is largely dominated by the so-called conjugated estrogens, the 3-sulfate esters from natural sources, since estrone and estradiol are not suitable for oral administration due to poor absorption and extensive metabolic inactivation. This ready metabolism also obtains when estradiol is administered parenterally. This shortcoming is partly overcome by more lipophilic derivatives of estradiol, which may themselves be devoid of estrogenic activity. These form a depot of the drug when injected subcutaneously in an oily medium. As the esters slowly leach into the circulation, endogenous esterases convert them to estradiol, providing relatively long-lasting levels of the biologically active compound. These fatty esters are prepared by straightforward esterification of estradiol with the acid chlorides of the desired acids. Relatively strenuous conditions are required to due to the fact that 17β alcohol is sterically quite hindered by the adjacent 18 methyl group; the 3,17 diacyl derivatives are consequently the initial products from this reaction. Exposure to a mild aqueous base leads to the saponification of the labile phenolic ester at the 3 position. The sequence with benzoyl chloride leads to **estradiol benzoate**, (**8-4**), and cyclopentylpropionic acid gives **estradiol cypionate** (**8-5**).

8-1

RCOCl

8-2, R = C_6H_6
8-3, R = $CH_2CH_2 cyclo C_5H_9$

$OH^{\ominus}$

8-4, R = C_6H_5
8-5, R = $CH_2CH_2 cyclo C_5H_9$
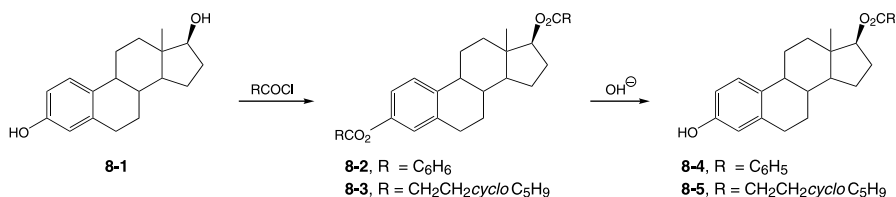
Absorption of orally administered, relatively lipophilic compounds, such as estrone or estradiol, occurs mainly in the intestine. The bacteria that colonize the gut are, however, particularly adept at converting those compounds by attack at the 17 position to very water-soluble derivatives that defy absorption. Alkylation of that position avoids this catabolic pathway and consequently enhances bioavailability on oral administration. The reaction of 17-keto steroids with nucleophiles illustrates the high degree of stereospecifity that is maintained in many steroid reactions; approach of that carbonyl group from the β face is virtually forbidden by the presence of the adjacent 18 methyl. The reaction products consequently consist of almost pure isomers from attack at the α face. Reaction of estradiol with lithium acetylide thus gives **ethynylestradiol** (**9-2**) [9]; the corresponding alkylation of estradiol 3-methyl ether (**9-1**) leads to **mestranol** (**9-3**) [10]. Both compounds are potent orally active

estrogens; the latter, as will be noted later, finds widespread use as a component of oral contraceptives. In a similar vein, reaction of estradiol with the lithium reagent from 2-iodofuran gives the adduct (**9-4**) as a single isomer. Acetylation with acetic anhydride leads to the orally active estrogen **estrofurate** (**9-5**) [11].

6-2, R = H
9-1, R = CH₃

9-2, R = H
9-3, R = CH₃

9-4

9-5
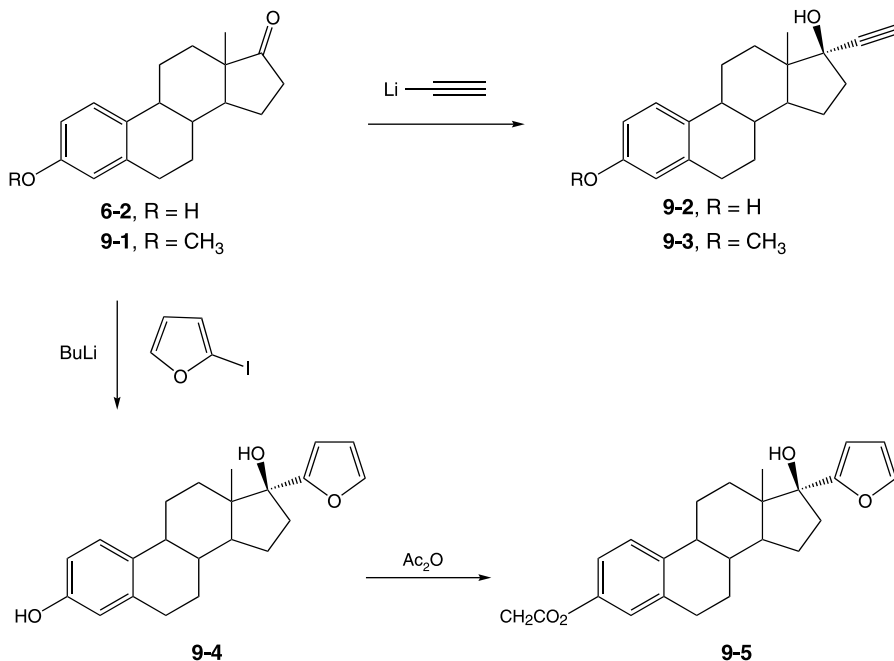
Only very subtle differences exist between cancer cells and their normal predecessors. The small divergences in genetic material and regulatory factors have so far proven beyond the reach of therapy. The bulk of cancer chemotherapy thus relies largely on kinetics, that is, on the fact that cells within neoplasms multiply far more quickly than do normal cells. The majority of chemotherapeutic agents in fact disrupt DNA in multiplying cells and thus affect them in preference to resting tissue. The so-called nitrogen mustard alkylating agents, which include a *bis*(chloroethylamino) group, have in fact been shown to react directly with DNA. Various attempts have been made over the years to achieve some organ specificity by attaching mustards to compounds that interact with tissue-specific receptors. The chemotherapeutic agent **estramustine** (**10-3**) is intended to steer an alkylating moiety to estrogen sensitive tissue by invoking the affinity of estradiol for estrogen receptors. The synthesis starts with the reaction of mustard (**10-1**) with phosgene to give carbamoyl chloride (**10-2**). Reaction of that with estradiol in the presence of a base leads to the product (**10-3**) [12]. The preferential formation of a phenoxide over an alkoxide combined with the more hindered nature of the 17-alcohol contributes to the selectivity.
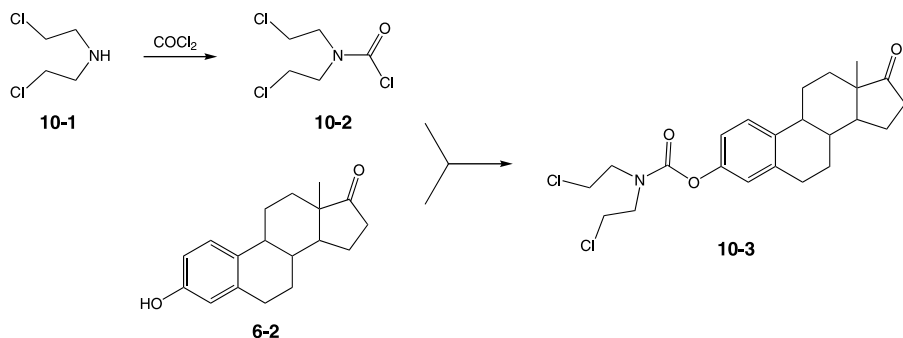
Virtually all known antiestrogens comprise nonsteroidal compounds based more or less closely on triphenyl ethylene (see Chapter 6). It is thus notable that a derivative of estradiol itself that carries a very unusual substituent also acts as an estrogen antagonist. Unlike its nonsteroid forerunners, the great majority of which show some measure of agonist activity, this agent is devoid of any estrogenic activity. The synthesis begins with conjugate 1,4 addition of the Grignard reagent from a long chain bromide (**11-2**) to the steroid 2,6-dienone 11-1 and affords the 7-alkylated product as a mixture of epimers at the new linkage. The 7α isomer (**11-3**) is separated from the mixture before proceeding; the hydroxyl group at the end of the long chain is then
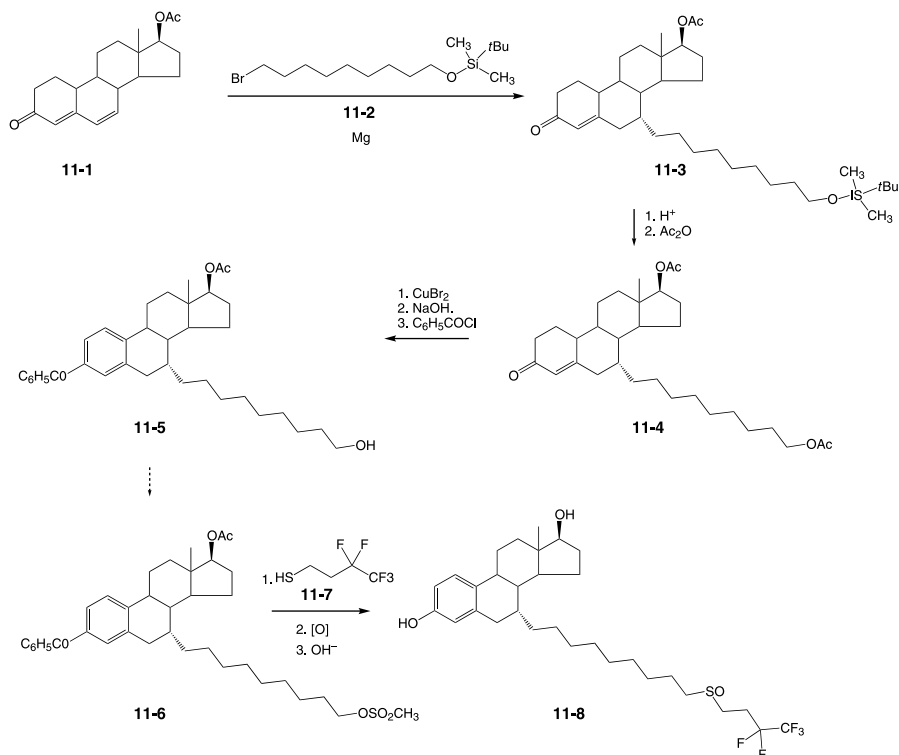
unmasked by hydrolytic removal of the silyl protecting group and the newly revealed hydroxyl acylated with acetic anhydride (**11-4**). Reaction with cupric bromide serves to aromatize ring A; saponification with a mild base preferentially removes the less sterically hindered acetate at the end of the long chain. Acylation by means of benzoyl chloride converts the phenolic hydroxyl at the 3 position to the corresponding ester (**11-5**) [13]. The synthetic route from this point on is speculative as details are not readily accessible. Reaction of this last literature intermediate (**11-5**) with methanesulfonyl chloride would then lead to mesylate (**11-6**). That group could then be displaced by sulfur on the fluorinated mercaptan (**11-7**). Controlled oxidation of sulfur, for example with periodate, would then lead to the corresponding sulfone. Saponification of the ester groups at the 3 and 17 positions would then afford the estrogen antagonist **fluverestant** (**11-8**). It might be noted that this specific compound is but one from a sizeable group of similarly substituted estradiol derivatives that show pure estrogen antagonist activity.

4.4. GONANES, THE 19-NOR STEROIDS

Steroids based on the estrane nucleus in which the formerly aromatic A ring occurs in reduced form are named as derivatives of the hypothetical hydrocarbon gonane. This very large class of compounds, which are more familiarly known as 9-nor steroids, has no counterpart in nature. It is thus of note that this group includes some very potent androgens, progestins, and, more recently, progesterone and corticosteroid antagonists. The original investigations of 19-nor steroids was spurred by the increasing availability of estrone as a starting material and the discovery by A. J. Birch of the eponymous method for reducing aromatic rings by means of dissolving metals in liquid ammonia [14].

4.4.1. Progestational Compounds

It was recognized by the 1940s that the high levels of circulating progesterone (**12-1**) that prevailed once pregnancy was established would inhibit subsequent ovulation. This was confirmed in rabbits where ovulation could be inhibited by injecting progesterone. The very poor absorption of orally administered progesterone frustrated attempts to use this as a method for inhibiting ovulation in women. The search for an oral contraceptive thus focused initially on finding orally active progestins.
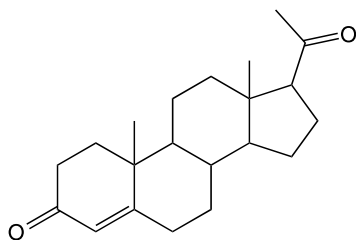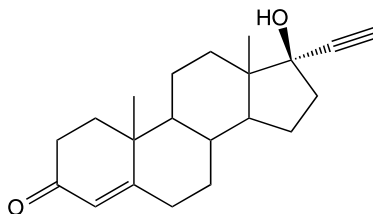
12-1   12-2

The observation that the ethynyl derivative of testosterone, **ethisterone** (**12-2**), exhibited progestational activity demonstrated that the acetyl side chain at the 17 position found in progesterone itself was not an absolute requirement for activity. It should be noted that the side chain in (**12-2**) has the opposite configuration from that of the acetyl in progesterone. Oral progestational activity had also been reported for 19-norprogesterone, obtained in minuscule yield by a lengthy degradation of a plant sterol. In one of those not infrequent coincidences, chemists working quite independently in the laboratories of Searle and Syntex took these cues as an incentive for the preparation of 17-ethynyl-19-norsteroids. Both compounds, norethynodrel (**13-5**) and **norethindrone** (**13-6**), eventually found widespread use as the progestational component of oral contraceptives.

Treatment of the methyl ether (**13-1**) of estradiol with lithium in liquid ammonia under the conditions of the Birch reduction leads initially to a radical dianion at the 1,4 positions, those being the sites of lowest electron density. Neutralization of the charges by the addition of ethanol gives the dihydrobenzene derivative (**13-2**) in which the future 3-keto group is present as its enol methyl ether. The hydroxyl group at the 17 position is then carefully oxidized using slightly basic Oppenauer conditions (**13-3**). Condensation with lithium acetylide occurs with the addition of the carbanion to the more open α face of the molecule to give the carbinol (**13-4**). Hydrolysis of the enol ether under mild conditions as, for example, oxalic acid gives the unconjugated ketone, **norethynodrel** (**13-5**) [15]. Hydrolysis of the ethynylation product (**13-4**) with mineral acid leads the double bond to shift to the conjugated 4,5 positions and the formation of **norethindrone** (**13-6**) [16].
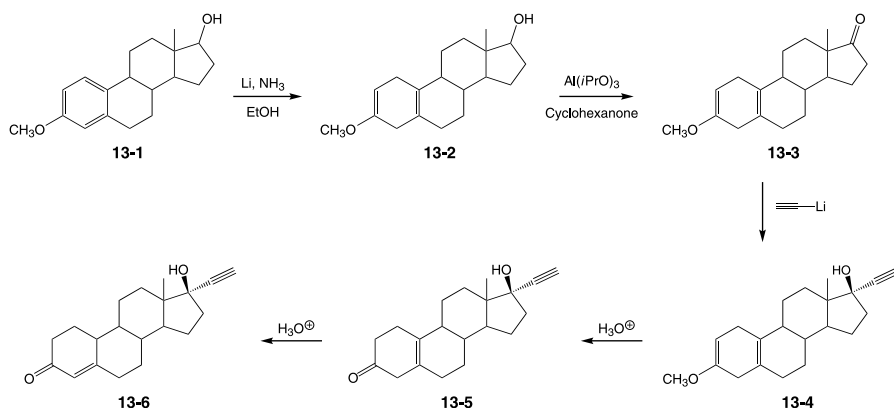
Clinical trials of these orally active progestins showed that they were effective as contraceptives with a success rate that exceeded 99%. These compounds were then marketed as obtained from the reaction sequence after appropriate purification. As the analytical methodology improved it became apparent that a small amount of an impurity was present in all active samples. An examination of the reaction scheme allowed ready identification of that by-product. Any unreduced estradiol methyl ether (**13-1**) will go to estrone methyl ether on oxidation; this will then afford the potent orally active estrogen **mestranol** (**9-1**) on ethynylation. Subsequent

investigation of **mestranol**-free **ethynodrel** suggested that estrogen was required for full efficacy. Virtually all commercial oral contraceptives today consequently consist of a progestational component admixed with a small controlled amount of **mestranol** or **ethynylestradiol**.

Oral progestational activity is retained when the ketone at the 3 position is reduced to an alcohol. Treatment of **ethindrone** (**13-6**) with the bulky reducing agent lithium aluminum-tri-*tert*-butoxy hydride leads to attack from the more open α face and the formation of the 3β hydroxy derivative (**14-1**). Acylation under forcing conditions affords the 3,17-diacetate derivative, **ethynodiol diacetate** (**14-2**) [17].
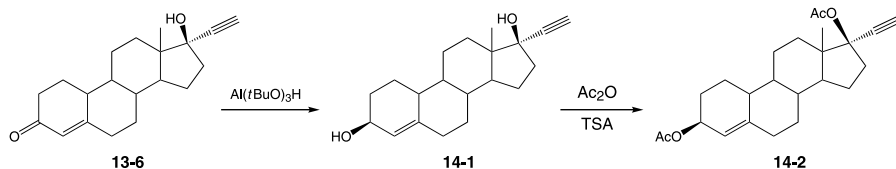
The compound in which the 3-keto group is reduced to a hydrocarbon interestingly still acts as an orally active progestin. The preparation of this compound starts with the hydrolysis of dihydrobenzene (**13-2**) to afford 19-nortestosterone (**15-1**). Reaction with ethane-1,2-thiol in the presence of catalytic acid leads to the cyclic thioacetal (**15-2**). Treatment of this intermediate with Raney nickel in the presence of alcohol leads to the reduced desulfurized derivative (**15-3**). The alcohol at 17 is then oxidized by any of several methods, such as chromic acid in acetone (Jones' reagent), and the resulting ketone (**15-4**) treated with lithium acetylide. There is thus obtained the progestin **lynestrol** (**15-5**) [18].
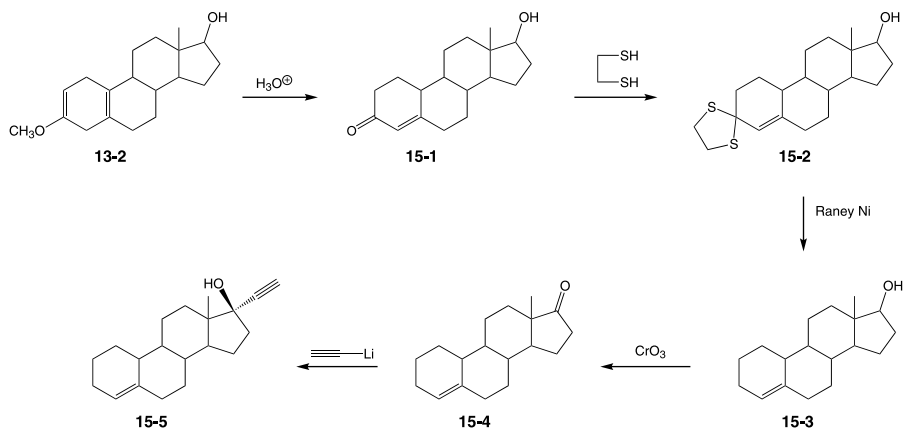
In much the same vein as above, hydrolysis of the enol ether (**13-2**) with a weak acid gives the unconjugated 5,9 olefin (**16-1**). This is then successively converted to a thioacetal, desulfurized, oxidized, and ethynylated. There is thus obtained the orally active progestin **tigestol** (**16-2**) [18].
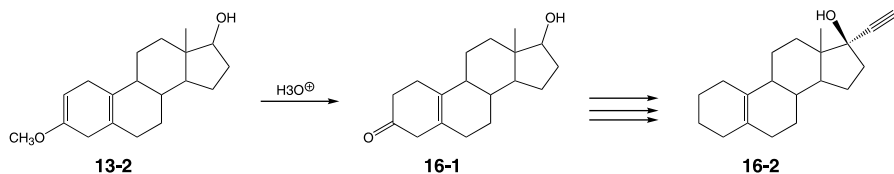
The oral progestin **norgestrel** (**17-4**) occupies an unusual place among steroid drugs in that it incorporates an angular ethyl group at the 18 position, a modification not accessible from the usual steroid starting materials. It was also one of the very few racemic steroid drugs when first introduced. It has been largely superseded by its resolved levorotatory isomer, **levonorgestrel**, which is about twice as potent. The compound is prepared by a modification on the Torgov-Smith scheme. Thus reaction of vinyl tetralol (**7-2**) with 2-ethylcyclopenta-1,3-dione (**17-7**) instead of the methylated dione gives the homologue (**17-2**) of the more usual intermediate. This is then subjected to the usual cyclization and reduction sequence to give the homologue (**17-3**) of estradiol 3-methyl ether. This last intermediate is then taken through the same sequence of steps used to prepare **norethindrone** (Birch reduction, oxidation, ethynylation, and hydrolysis) to afford, finally, **norgestrel** (**17-4**) [19].
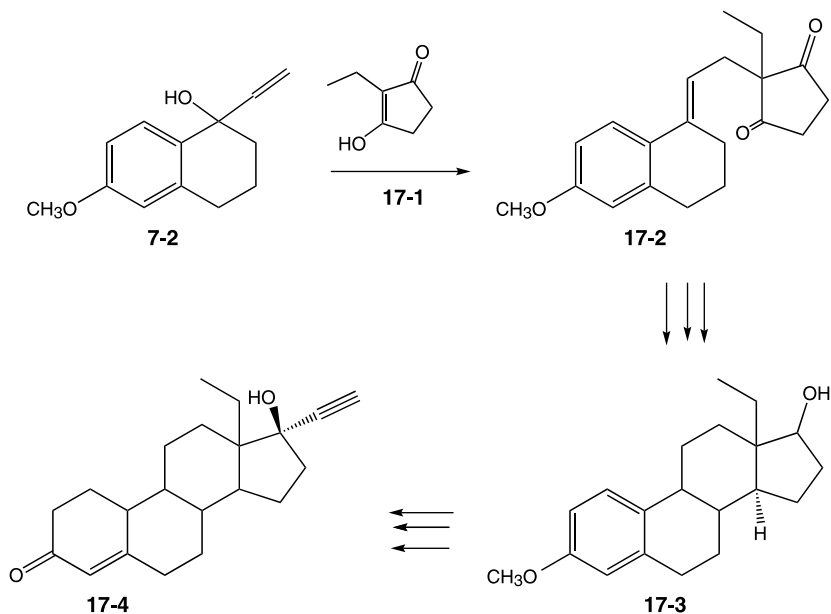
The almost immediate commercial success of the gonane-based oral contraceptives spurred an impressive amount of work in this series aimed at developing new market entries. Describing each of those in detail is beyond the scope of this volume; instead, we present below some examples chosen almost arbitrarily because their synthesis involves some interesting chemistry.

The key intermediate (**18-1**) in the preparation of **gestodene** (**18-5**) is obtained by Birch reduction of the methyl ether of 18-methylestradiol (**17-3**) from total synthesis, followed by hydrolysis to the conjugated ketone and the subsequent oxidation to a diketone. The distinguishing feature of this compound, unsaturation at 15,16, is introduced by biotransformation. Thus, fermentation of diketone (**18-1**) with *Penicillium raistricki* introduces a hydroxyl group at the 15α position (**18-2**). Reaction of the product with neopentyl glycol proceeds to form an acetal of the ketone at the sterically more accessible 3 position. This reaction affords a mixture of unrearranged 4,5 olefin and the product in which the olefin has shifted to the 5,9 position. The alcohol at the 15 position is then converted to its mesylate (**18-3**). Treatment with a base such as triethylamine results in elimination to give the conjugated ketone (**18-4**). Addition of lithium acetylide followed by removal of the acetal by hydrolysis affords **gestodene** (**18-5**) [20].
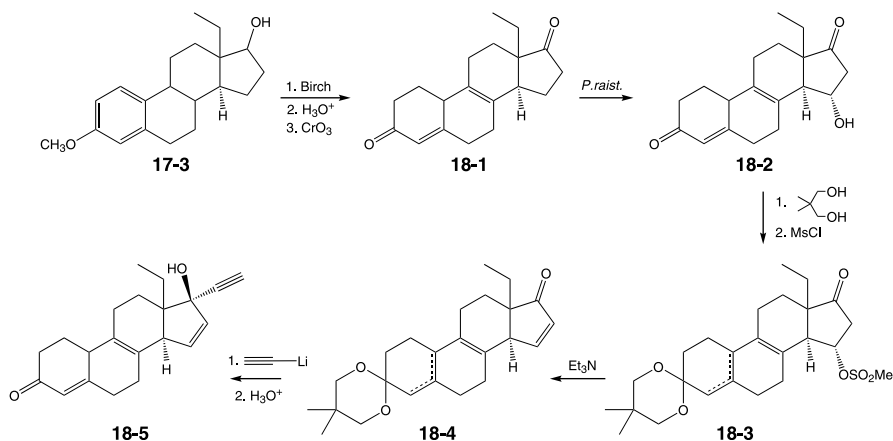
Ethynerone (**19-4**) differs from the prototype progestins in that it incorporates a chloroacetylene moiety as well as an extended conjugated diene. Reaction of *cis* 1,2-dichloro-ethylene with lithium metal involves elimination of the elements of hydrogen chloride and formation of chloroacetylene as the first step; that intermediate again reacts with lithium to form an acetylide anion. Addition of that to the 17 ketone in **norethynodrel** intermediate (**13-3**) gives the corresponding carbinol (**19-1**). Hydrolysis of the acetal under mild acidic conditions affords the unconjugated ketone (**19-2**). That intermediate is then treated with bromine and pyridine. The first step almost certainly involves the addition of bromine across the 5,9 double bond to give a *trans* dibromide of unspecified stereochemistry (diaxial opening of an initial α bromonium ion, for example, would give the 5α,10β isomer). The dibromide loses hydrogen bromide in the presence of pyridine to give diene (**19-4**) and thus **ethyner-one** (**19-4**) [21]. The stability of this compound is surprising in view of the fact that it is at the oxidation state of a phenol.
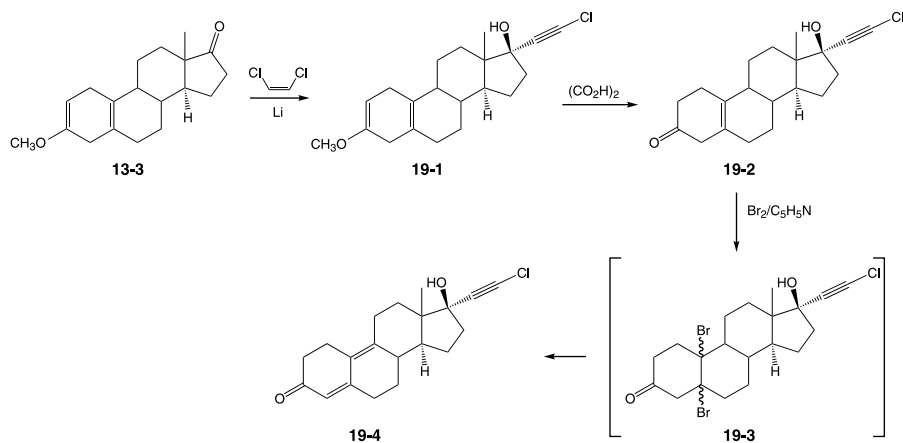
The presence of substituents at the relatively inaccessible 11 position in ring D has been found to increase potency in both estrogens as well as progestins in the gonane series. The synthesis of a 19-nor compound that incorporates a methylene group at that location starts with alkylation of the hydroxyl at position 17 in the norgesterel intermediate (**20-1**) with benzyl chloride. Treatment of that intermediate with acid results in migration of the styrene double bond from the 8,9 ring fusion position to the 9,11 carbons in ring C (**20-3**) that intermediate (**20-2**) with acid; this in effect provides a handle for functionalizing the otherwise inert carbon at 11. Thus, reaction of that compound with diborane, followed by treatment of the initial adduct with hydrogen peroxide, introduces a hydroxyl group at position 11 (**20-4**). The newly introduced alcohol is next oxidized by means of chromyl chloride in pyridine to afford the corresponding ketone (**20-5**). Condensation of that intermediate with methylmagnesium bromide proceeds to afford the product (**20-6**) from the addition of the reagent from the more open α face of the molecule.
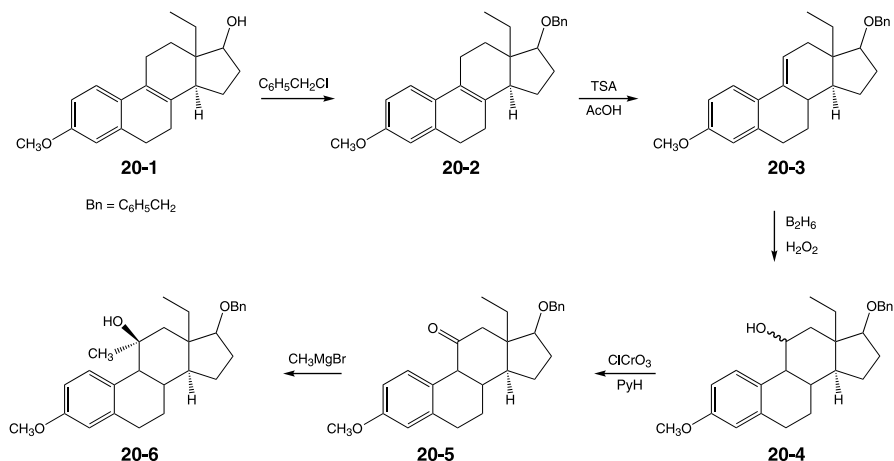
Treatment of this last intermediate with lithium in liquid ammonia and *tert*-butanol reduces the aromatic A ring to the 1,4-dihydrobenzene stage; the benzyl ether at position 17 is cleaved reductively at the same time. The newly exposed hydroxyl group is

then oxidized to afford the 17 ketone (**21-1**). Toluenesulfonic acid in formic acid leads to the elimination of the tertiary hydroxyl at position 11 with the concomitant formation of an exomethylene group. The carbonyl group at position 3 is significantly more reactive than the sterically encumbered ketone at 17, requiring that the former be inactivated in order to add substituents to the 17 position. Thus, reaction of the diketone (**21-2**) with pyrrolidine proceeds selectively at position 3 to afford enamine (**21-3**). Reaction of this last intermediate with lithium acetilide leads to addition at position 17. Treatment of the adduct with an aqueous acid hydrolyzes the enamime. There is thus obtained **etonorgestrel** (**21-4**) [22].
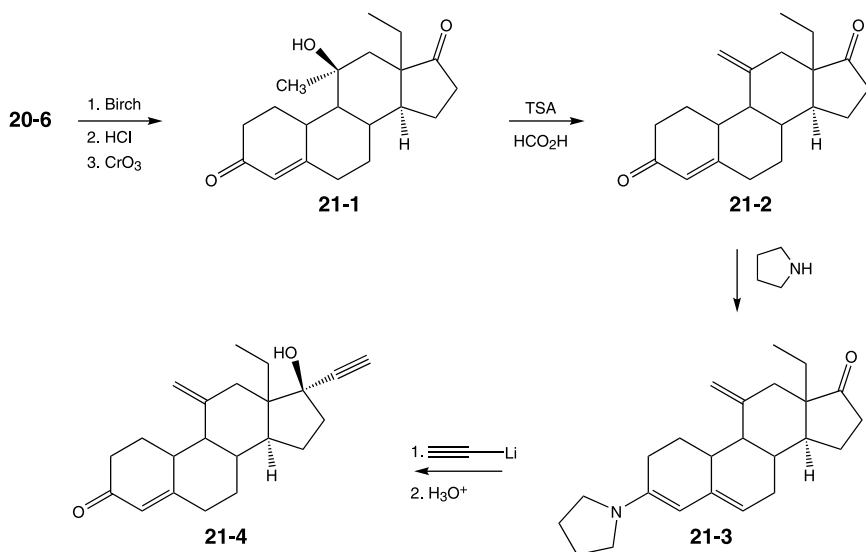
The 5,9–10,11 gonane (**24-4**) was first prepared as an intermediate to a 4,9,11-triene progestin, **norgestrienone**, which was never commercialized in the United States. The synthesis is, however, of interest since (**24-4**) serves as starting material for two progesterone antagonists discussed later in this chapter. The total synthesis used to prepare this compound differs from the Torgov–Smith route in that three of the rings are constructed sequentially; the presence of an intermediate carboxylic acid in the scheme permits resolution at a relatively early stage. The synthesis starts with Robinson-type annulation of cyclopentadione (**7-2**) with the methylvinyl ketone derivative (**22-1**) to give the hydrindone (**22-2**). Catalytic reduction of the double bond establishes the all-important *trans* stereochemistry for the CD ring fusion. The fragment that will form ring B is attached to an enolizeable position that will be altered later in the synthesis [23]. The cyclopentane carbonyl group in product (**22-3**) is reduced to an alcohol while temporarily protecting the more accessible cyclohexanone as its acetal. Acylation of the newly formed hydroxyl affords benzoate (**22-4**); this is then converted to cyclic enol lactone (**22-5**) with acetic anhydride. Condensation of the enol lactone with the Grignard reagent from protected 1-bromo-4-pentanone (**22-6**) affords a product (**22-7**) from a reaction that formally consists of replacing the ring oxygen by carbon.
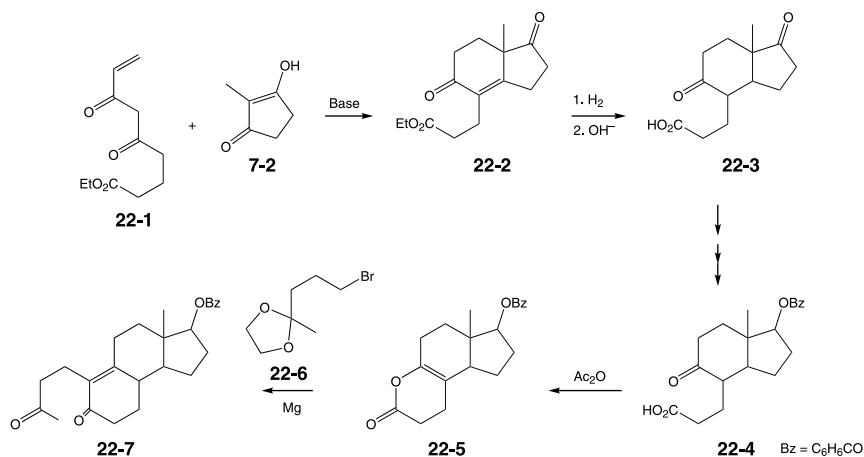
The sequence can be rationalized by assuming that only a single organometallic adds to **A** to give the lactol **B** as a magnesium salt. The usual acid workup of the product will then proceed at least transiently to lactol **B** to give diketone **C**. Acid cyclization will then afford a cyclohexanone, **D**; in the case at hand, further hydrolysis of the side chain protecting group leads to the observed product (**22-7**).
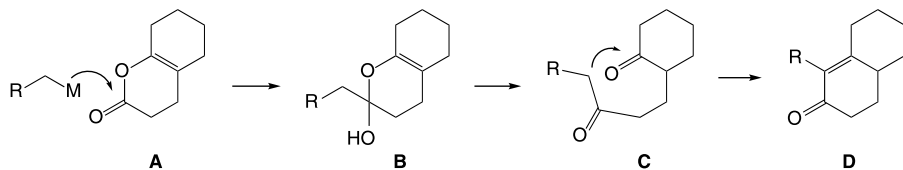
Reaction of the diketone (**22-7**) with piperidine leads to the formation of an enamine at the side chain carbonyl group (**24-1**). The nucleophilic terminal
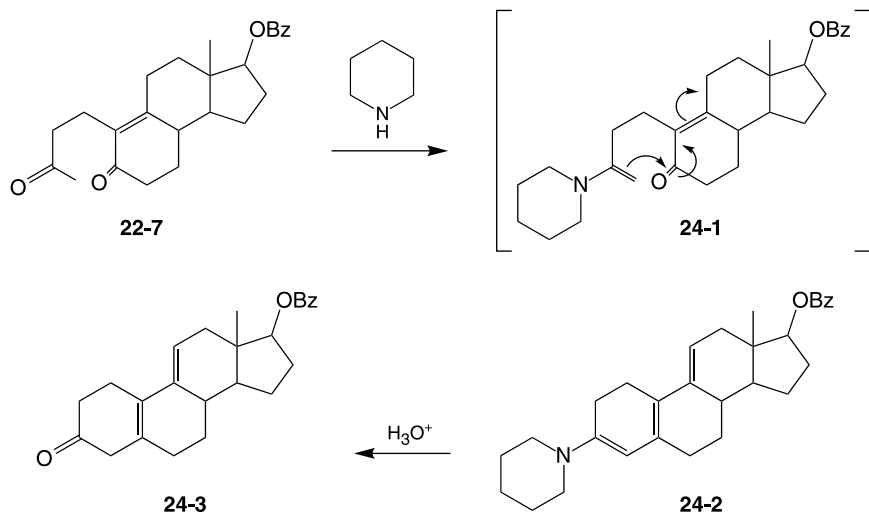
methyne then adds to the ring carbonyl to effect cyclization; the double bond presumably shifts in the course of the reaction; enamine (**24-2**) is thus obtained as an isolable intermediate. Acid catalyzed hydrolysis of the eneamine affords the desired steroid intermediate (**24-3**) as a single enantiomer [24].

We have already seen that **ethisterone**, in which the side chain at the 17 position consists of an ethynyl group in the α position combined with a β hydroxyl, has the same biological activity as progesterone, which has a β-acetyl side chain. It is interesting that this analogy carries over to the gonane series as does the improved potency noted in the natural series when an α hydroxyl is added to progesterone. The synthesis of the gonane analogue starts with the diosgenin degradation product (**2-4**). Saponification of the acetyl group at the 3 position, followed by Oppenauer oxidation of the resulting alcohol, affords 16-dehydropregnenolone (**25-1**). This is then converted to the 1,4-dienone (**25-2**) by the usual sequence involving bromination and dehydrohalogenation. This compound is then converted to its A-ring aromatic counterpart by one of several methods, such as treatment with lithium metal in the presence of diphenylmethane as a buffer. Methylation of the newly formed phenol by means of methyl iodide and a base affords the methyl ether (**25-3**). The 15,16 double bond of the enone is then converted to its epoxide (**25-4**) by means of basic hydrogen peroxide; the less hindered milieu of the α side determines the stereochemistry of epoxide formation. The first step in the reaction with hydrogen bromide involves protonation of the epoxide oxygen. Examination of this intermediate suggests that attack by bromide at the 16 position is highly favored for steric reasons; the fact that the product consists of the 16β-bromo-17-α-hydroxy derivative (**25-5**) bears out that supposition.
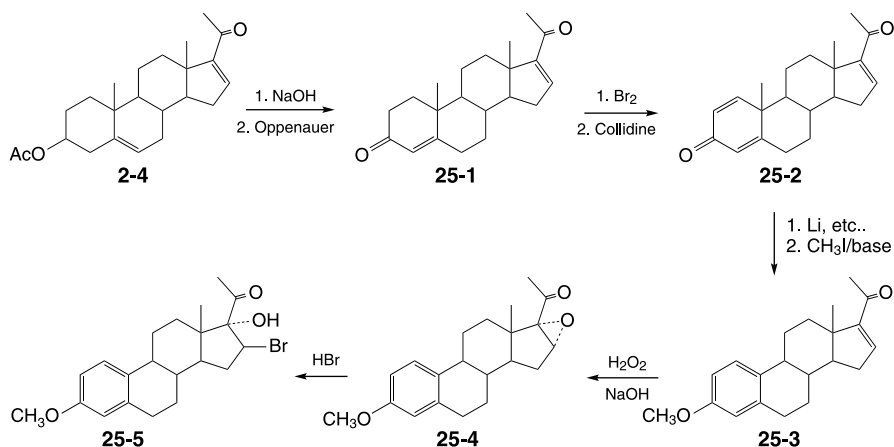
The superfluous bromine is then removed by reduction with zinc in acetic acid (**26-1**). The 20 ketone is next protected against the strongly reducing conditions in the subsequent step by conversion to the ethylene glycol acetal (**26-2**). Birch reduction with lithium in liquid ammonia in the presence of ethanol proceeds as usual to the dihydrobenzene (**26-3**). Treatment of this last product with mineral acid serves to hydrolyze both the enol ether at the 3 position and the acetal at the

20 position; the double bond shifts into conjugation as well. There is thus obtained **gestonerone** (**26-4**) [25]. This compound is used in the clinic as its 17-caproate ester.
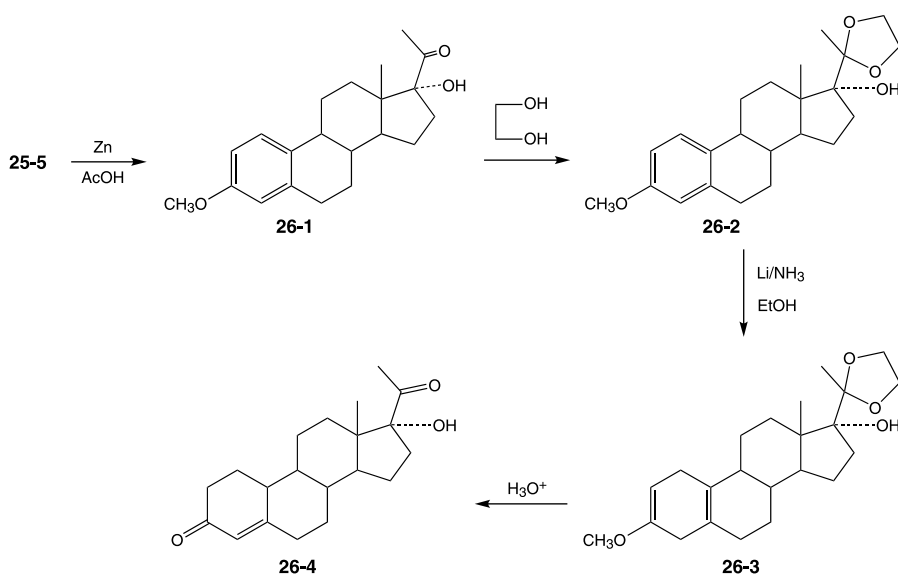
4.4.2. Progesterone Antagonists

Important drug classes have often come from the ranks of compounds that show antagonist activity against endogenous hormones or messenger substances; the β-blockers, which provide a prime example, have been discussed in Chapter 2. The estrogen antagonists for many years comprised the only examples of compounds that antagonized steroids by binding to estrogen receptors; these compounds, whose structures only superficially mimic steroids, are discussed in Chapter 6. The discovery of the next class, the progesterone antagonists, which also shows some antiglucocorticoid activity, was probably due in part to the availability of intermediates for totally synthetic gonane progestins [26]. The first clinically successful progesterone antagonist, **mifepristone** (**28-3**), attracted public attention under the manufacturer's code name RU-486. Considerable controversy still exists over the use of the drug as a contraceptive. Whereas the progestin agonists prevent ovulation, the antagonists deprive the lining of the uterus of progestational stimulation required for successful implantation and maintenance of a fertilized ovum; this in effect results in early abortion. This outcome is aided in practice by the subsequent administration of a prostaglandin; the latter typically consists of **misoprostol** (see Chapter 1).

The synthesis of the first of these antagonists, **mifepristone** (**28-3**), starts by conversion of the intermediate (**24-2**) to the corresponding 3,17 diketone by sequential saponfication of the benzoate at 17 and oxidation of the resulting alcohol. Reaction of the compound with ethylene glycol proceeds preferentially at the 3 position to

give the 3-ethylene acetal (**27-1**). The ketone at 17 is then protected as a silylated cyanhydrin. Thus treatment of (**27-1**) with trimethylsilyl cyanide leads to the formation of the silylated cyanohydrin at the 17 position to afford (**27-2**). Oxidation of this with the adduct from hexafluoracetone and hydrogen peroxide occurs selectively at the 5,9 double bond, affording the α-epoxide (**27-3**). Attack from the somewhat less hindered face of (**27-2**) accounts for the stereochemistry; the regiochemistry may be controlled by proximity of the acetal oxygen. Reaction with the Grignard reagent from 4-bromodimethylaniline results in what can be viewed as a vinylogous oxirane opening. The organometallic thus approaches the 11 terminal of the olefin from the same side as would be required for a *trans* diaxial opening of the oxirane, or, more probably, a magnesium salt complex of the oxirane. Bond reorganization will then lead to the observed product (**27-5**).
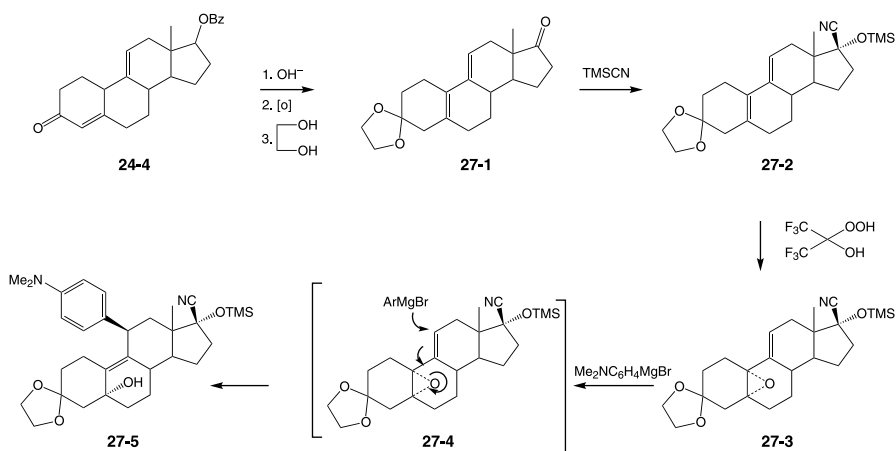
The protecting group at the 17 position is then removed by hydrolysis under weakly acidic conditions to give the corresponding 17 ketone (**28-1**). That is then reacted with propargyl lithium to afford the diol (**28-2**). Hydrolysis of this last intermediate in the presence of a strong acid first removes the acetal group at position 3; the resulting β-hydroxyalcohol then dehydrates to give the 4,9 conjugated dieneone. There is thus obtained **mifepristone** (**28-3**) [27].
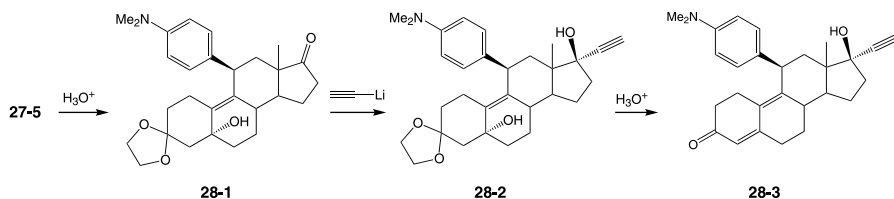
A recent compound in this class, **asoprinosil** (**29-9**), is a more selective antagonist of progesterone and also shows reduced binding to glucocorticoid receptors. Treatment of the diene (**29-1**), a total-synthesis product-derived 19-nor gonane, with hydrogen peroxide results in selective reaction at the 5,10 double bond to

give the epoxide (**29-2**). The proximity of the acetal oxygens at the 3 position accounts for the regiochemistry of the product; attack from the more open α side accounts for the stereochemistry. Condensation of (**29-2**) with the Grignard reagent from the methyl acetal of *para*-bromobenzaldehyde (**29-3**) in the presence of cuprous salts leads, as in the example above, to a conjugate addition to the 11 position with a concomitant shift of the double bond to the 5,9 positions (**29-4**). Construction of the side chain at the 17 position starts with the addition of the ylide from trimethyl-sulfonium iodide to the carbonyl group to give the oxirane (**29-5**). Reaction of the product with sodium methoxide opens the epoxide ring to give the ether alcohol (**29-6**). Alkylation of the hydroxyl group at 17 with methyl iodide and a base affords the *bis* methyl ether (**29-7**). Exposure of that intermediate to acid leads to the hydrolysis of the acetal protecting groups on the ketone at 3 as well as the aromatic aldehyde; the tertiary alcohol on the AB ring junction dehydrates under those conditions, restoring the double bond (**29-8**). Reaction of this last intermediate with hydroxylamine leads to the formation of the aldoxime in a 95 : 5 E to Z ratio. The purified isomer **asoprinosil** (**29-9**) [28] is currently in the clinic as a treatment for endometriosis as well as other conditions related to undesirably high progesterone stimulation.
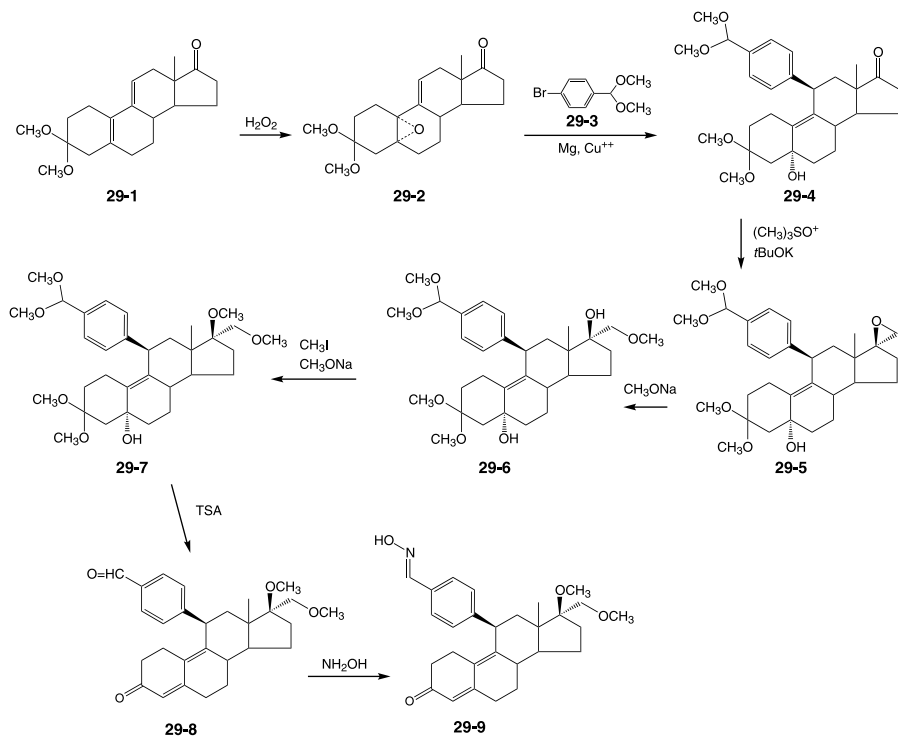
The synthesis of the progestin antagonist **onapristone** (**31-2**) also starts with the saponification product from (**24-2**). In this case, the intermediate is first converted to a 3,3-dimethylpropylene acetal by reaction with neopentyl glycol; oxidation as

above with the hydroxy hydroperoxy acetal of perfluoroacetone gives the 5α,9α oxirane (**30-1**). Condensation with the Grignard reagent from 4-bromo-*N,N*-dimethylaniline proceeds as above to give the 1,4 addition product (**30-2**). The route diverges markedly from that described above in the next step. Thus, photolysis of (**30-2**) gives a product of inversion of position 13; the transformation can be rationalized by assuming the photolytic scission of the 13,14 bond to give an intermediate diradical such as (**30-3**). Ring closure to a thermodynamically favored *cis* hydrindanone will lead to the observed product (**30-4**).
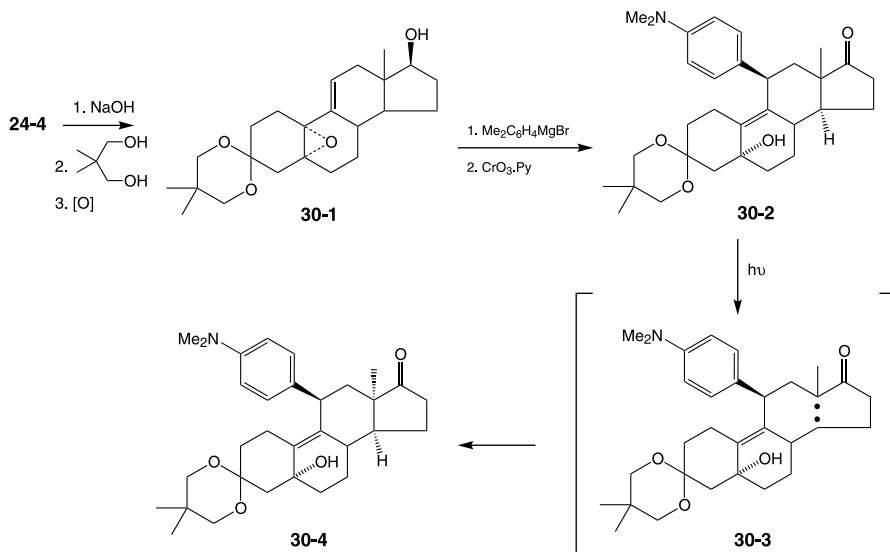
The altered stereochemistry about the 17 ketone interestingly reverses the direction of additions to that carbonyl group. Thus, condensation of (**30-4**) with the Grignard reagent from the tetrahydropyranyl ether of 3-bromopropan-1-ol gives the product (**31-1**) of addition of the organometallic from the β face rather than the customary α face. Hydrolysis of this last intermediate with a strong acid results in the loss of the protecting groups as well as the dehydration of the hydroxyl group at the 4 position; there is thus formed **onapristone** (**31-2**) [29].
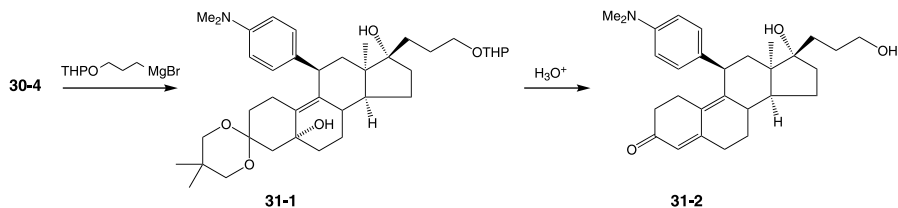
4.4.3. Androgenic Compounds

The clinical success of the progestational gonanes engendered a corresponding effort toward finding potent orally active androgens in the 19-nor steroid series. The

prototype in this series is testosterone. This endogenous hormone, or, more properly, its active metabolite, 5α-dihydrotestosterone, plays a pivotal role in supporting male reproductive function as well as the integrity of sexual organs. The immediate indication for these androgens is of course replacement therapy. More important from the commercial viewpoint is the fact that many androgens also serve as anabolic agents; that is, they modify the utilization of nutrients so as to conserve nitrogen and thus build muscle mass. The misuse of androgens, commonly referred to simply as "steroids" by athletes, is the subject of many current news stories. The reputed widespread abuse of these steroids has led to the inclusion of a lengthy roster of natural and synthetic androgens to the Drug Enforcement Agency (DEA)'s list of controlled substances, a list at one time reserved for narcotics and psychoactive compounds.

The gonane that most directly corresponds to testosterone shows full activity as an androgen. This compound, **nandrolone**, is prepared in a straightforward manner from estradiol-3-methyl ether, which is itself obtained from estrone (**9-1**) by reduction of the 17 ketone. Birch reduction of that intermediate followed by acid hydrolysis of the first-produced enol ether gives **nandrolone (32-1)**. This compound is seldom used as such because of its ready inactivation *in vivo*, but is used instead as a starting material for injectable derivatives. Esterification of the 17 hydroxyl group with any of several lipophilic acids gives oil-soluble derivatives. These are administered by subcutaneous injection so as to form depots; an esters that slowly diffuses into the blood stream from the depot is saponified to **nandrolone** by serum esterases. This results in long-lasting blood levels of the drug. A typical example of one of those drugs is **nandrolone decanoate (32-2)**, obtained by esterification with decanoyl chloride [30].

One of the important mechanisms by which orally administered steroids are inactivated involves the formation of water-soluble derivatives at the 17 position, a process that is greatly reduced in 17α-alkyl-17β-hydroxy derivatives. Extensive use of the resulting orally active compounds has since revealed that 17 alkylation also leads to increased liver toxicity. Preparation of the first of these compounds, **normethandrolone (32-3)**, starts by addition of methylmagnesium iodide to estrone methyl ether (**9-1**) to give the 17α methyl derivative. Birch reduction followed by acid hydrolysis leads to **normethandrolone (32-3)** [16].

The synthesis of the homologue **norethandrolone** starts with catalytic reduction of the side chain unsaturation in mestranol (**9-1**) to the corresponding ethyl derivative
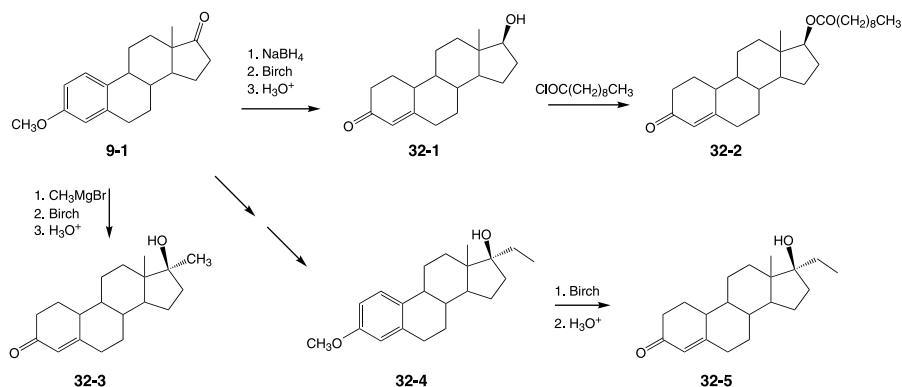
(**32-4**). Birch reduction followed by acid hydrolysis gives the orally active androgen **noerethandrolone** (**32-5**) [10].

The addition of a methyl group at the 7α position results in a major increase in potency in 19-nor androgens. The key dienone (**33-1**) is obtained by dehydrogenation of the 17 acetyl derivative of **nandrolone** (**32-1**) with chloranil (1,2,4,5-tetrachloro-benzoquinone). Condensation of that intermediate with methylmagnesium bromide in the presence of cuprous iodide results in 1,6 addition of the organometallic to give the 7α methyl derivative (**33-2**), possibly via the intermediacy of a cuprate reagent. The stereochemistry can be rationalized by assuming an approach from the more open face of the molecule. The alcohol at the 17 position is then oxidized to the corresponding ketone (**33-3**), typically with Jones' reagent. In order to direct an additional methyl group to the carbonyl group at the 17 position, the ketone at 3 must first be protected. Thus, reaction with pyrrolidine results in the preferential formation of an eneamine at 3 (**33-4**) due to the greater steric hindrance about the 17 ketone. Reaction of (**33-4**) with methyl Grignard reagent followed by removal of the enamine by acid hydrolysis affords the potent, orally active androgen, **mibolerone** (**33-5**) [31].
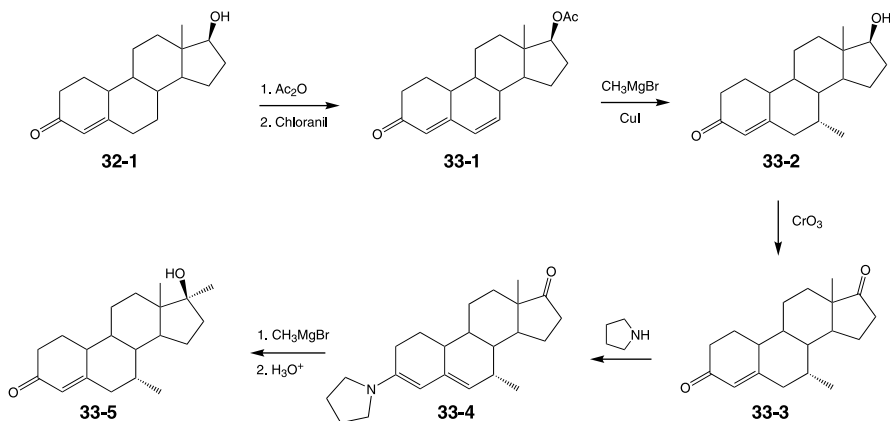
4.5. ANDROSTANES

Steroids that possess angular methyl groups at both the 10 and 13 positions but which are devoid of acetyl side chains at the 17 position are usually classed as derivatives of the hypothetical hydrocarbon, androstane. The endogenous male sex hormones, such as, for example, testosterone, can all be classified as androstanes; as will be noted below, the biological activity of compounds in this structural class goes beyond that narrow definition.

4.5.1. Starting Materials

The androstane nucleus is sufficiently complex so as to effectively rule out total synthesis as a commercial source for starting materials. The great preponderance of steroid natural products includes carbon side chains at the 17 position. Preparation of androstane starting compounds thus relies on schemes for degrading those side

chains. One route for the preparation of the key intermediate, dehydroepiandrosterone (**34-4**), starts from 16-dehydropregnenolone acetate (**2-4**), itself derived from *dios-genin*. (Androsterone differs from (**34-4**) in that the 3-hydroxyl has the α configuration, hence *epi*, and the compound includes the 5,6 olefin, hence *dehydro*.) Reaction of that compound with hydroxylamine hydrochloride in the presence of a base leads to the oxime (**34-1**). Treatment with a strong acid results in the Beckmann rearrangement of the isonitroso group to afford the enamine acetate (**34-2**), which is seldom isolated; saponification with a base leads to the formation of an intermediate primary enamine as well as the loss of the acetate at the 3 position. Subsequent treatment of (**34-3**), which may exist as the 17-imine, with mild acid leads to hydrolysis of that group to a 17 ketone, to afford dehydroepiandrosterone (**34-4**) [32]. It might be noted that endogenous testosterone is in fact derived from this compound by metabolic transformation; this is probably the main reason that dehyro-epiandrosteron (**34-4**) has gained some popularity as a health food supplement under the label DHEA.
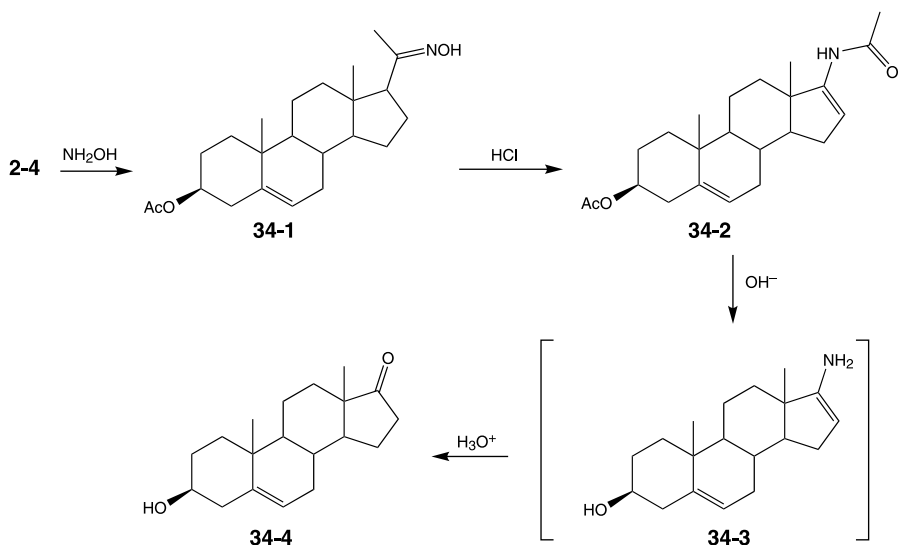
4.5.2. Androgenic Compounds

One of the very early derivatives in this series, as in the case of estrogens, was designed to circumvent the inactivation of orally administered compounds by metabolic transformation about the 17 position by adding steric hindrance by way of a methyl group. Thus reaction of (**34-4**) with methylmagnesium bromide gives the product (**35-1**) from addition from the α face. Reaction of the product with aluminum isopropoxide in the presence of cyclohexanone (Oppenauer oxidation) serves to oxidize the alcohol at the 3 position; the double bond shifts into conjugation under reaction conditions. There is thus obtained the orally active androgen **methyltestosterone** (**35-2**) [33].

The presence of additional methyl groups at a variety of positions increases oral potency in the androgenic 17-methyltestosterone series, as was the case in the gonane series noted previously (see mibolerone, **33-5**). In much the same vein, dehydrogenation of the conjugated enone (**34-4**) with chloranil gives the dieneone (**35-3**). The addition of methylmagnesium bromide in the presence of cuprous iodide gives predominantly the 7α methyl derivative, **bolasterone** (**35-4**), which shows potent androgenic and anabolic activities [34]. The 7β isomer is a minor product; this compound **calusterone** (**35-5**), which can be isolated from the mixture, has been used in the treatment of breast cancer.
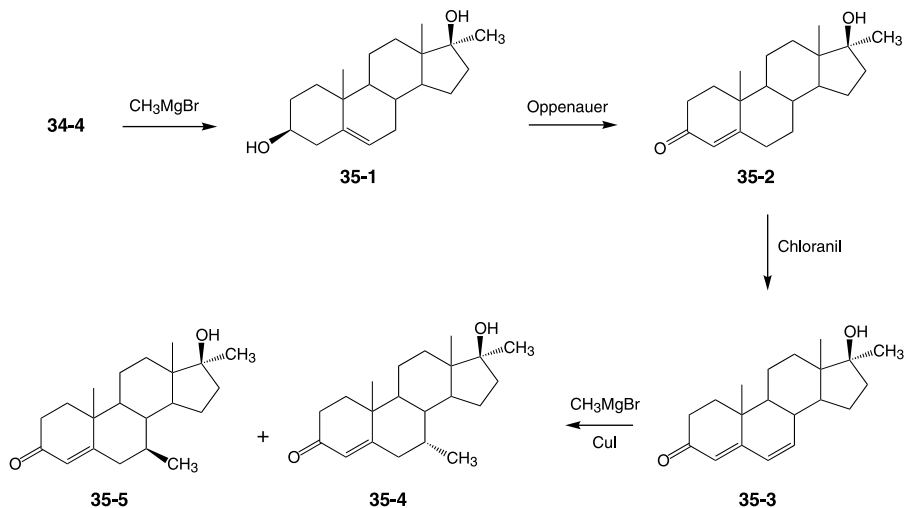
The 2-formyl derivative (**36-4**) from androstanone provides the key intermediate for entry to androgens bearing an additional fused heterocyclic ring as well as
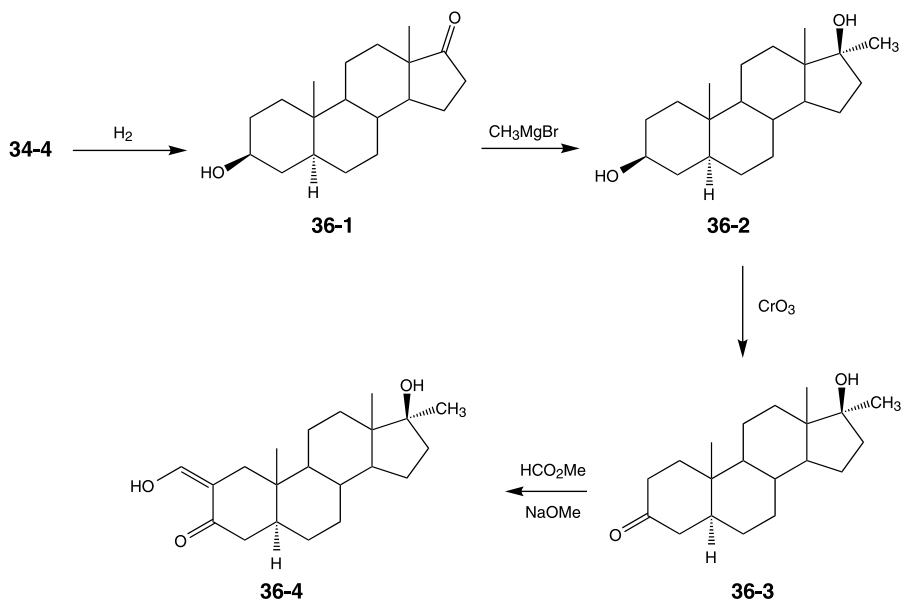
derivatives methylated at the 1 or 2 position. Preparation of this intermediate starts with the reduction of dehydroepiandrosterone (**34-4**) to give the 5α-dihydro deriva- tive (**36-1**). This is then condensed with methylmagnesium bromide to give (**36-2**); oxidation of the hydroxyl at the 3 position by one of a number of reagents, such as Jones', gives the dihydrotestosterone derivative (**36-3**). Though 3 ketone can of course form enolates at either the 2 or 4 position, reactions involving that at the 2 pos- ition are favored. Sodium methoxide-mediated condensation with methyl formate thus affords exclusively the product (**36-4**) from formylation at the 2 position [35].

Catalytic hydrogenation of the formyl derivative (**36-4**) proceeds as usual from the more open α face of the molecule to afford the axial 2β methyl derivative (**37-1**). Treatment with a strong base leads to epimerization to the more stable equatorial 2α methyl isomer. There is thus obtained the androgen, **dromostanolone** (**37-2**) [35]. The compound is used clinically as its 17-propionate ester. Direct reac- tion of the formyl ketone (**36-4**) with hydrazine leads to the formation of a fused pyrrazole ring [36]; this product is the widely used androgenic and anabolic drug, **stanazole** (**37-3**).
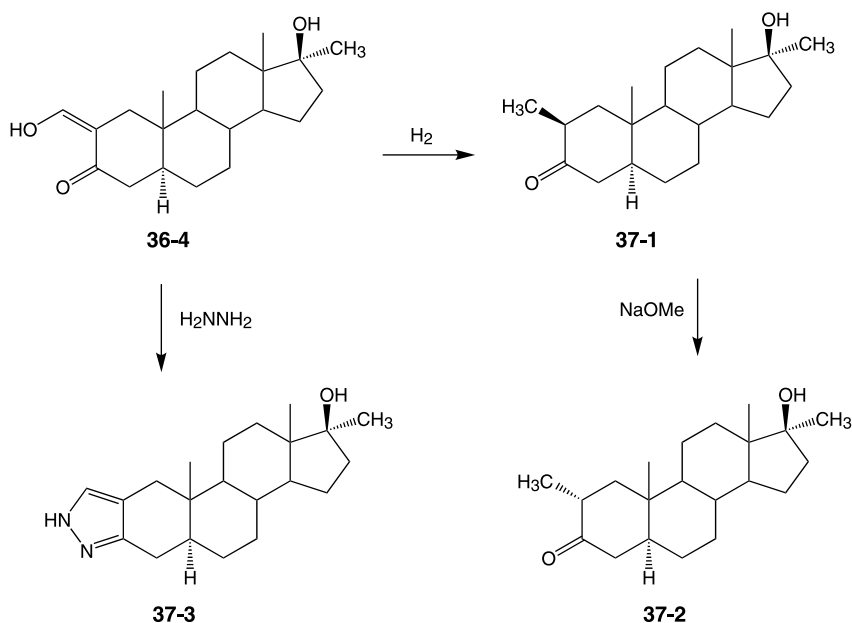
One of the more important functions in the male of androgens consists in support of reproductive function and male accessory organs. This stimulating function can, however, have deleterious effects; it has been known for many years that androgen stimulation is responsible for benign prostatic hypertrophy, a condition suffered by close to half of all men as they age. There is also considerable evidence to indicate that androgens exacerbate prostatic cancer. The search for an effective antiandrogen has thus been the focus of considerable effort over the years. The replacement of hydrogen on the heterocycle by a strong electron-withdrawing group in conjunction

with the substitution of the methyl at 17 by ethynyl leads to a compound that acts as an antagonist at the androgen receptors. The starting material (**38-1**) is obtainable by a scheme analogous to that used to obtain (**36-3**) from (**36-1**). Condensation of (**38-1**) with methyl formate in the presence of sodium methoxide leads, as above, to the ketone bearing a formyl group at the 2 position. The hydroxyl group is next acylated by sequential reaction with thionyl chloride and acetic anhydride so as to increase its reactivity (**38-3**). Reaction of that product with hydrazine mono-mesyalte leads to the formation of a substituted pyrrazole ring (**38-4**) and thus the antiandrogen **zanoterone** [37].
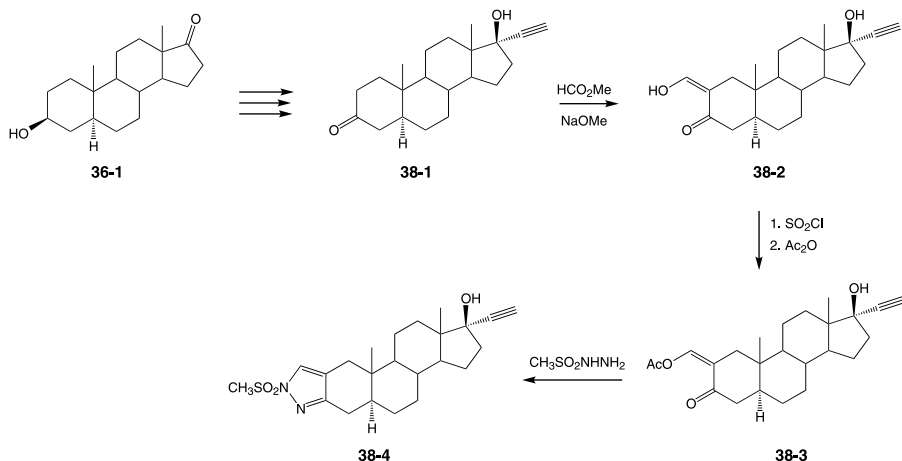
Careful investigation of the bromination reaction of 3 keto steroids, which leads ultimately to 2,4-dibromo derivatives (see, for example, **5-2–5-3**), revealed that the sequence starts with the formation of a 2α bromo derivative, a futher demonstration of the preferred enolization of the carbonyl group toward the 2 position.
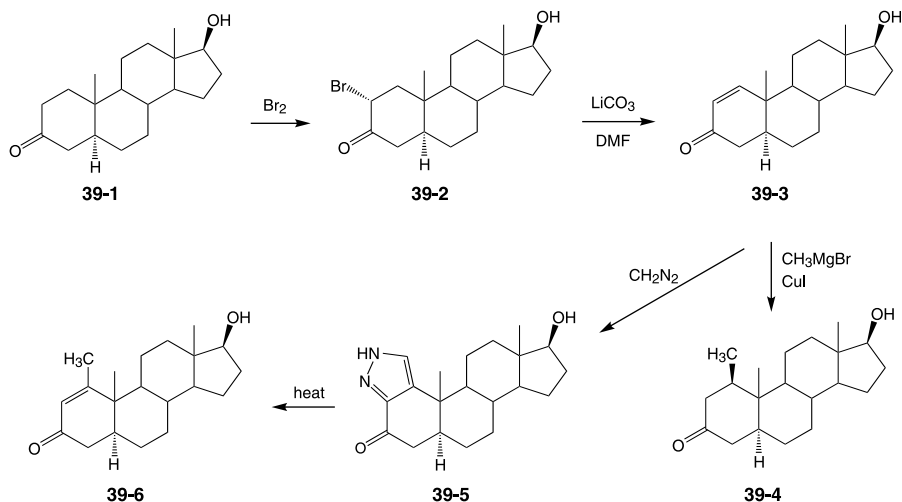
Thus the treatment of ketone (**39-1**) with one equivalent of bromine under carefully controlled conditions afford 2α bromide (**39-2**). The bromoketone is then dehydro-brominated by means of lithium carbonate in dimethyl formamide to give the unusual enone (**39-3**). The conjugate addition of methyl Grignard reagent in the presence of cuprous iodide goes directly to the 1β methyl derivative **mesterolone (39-4)** [38]; the reaction in this case goes directly to the energetically favored equatorial isomer. One of the standard methods for preparing fused cyclopropanes involved 1-3 dipolar addition of diazomethane to an olefin followed by pyrolysis of the resulting pyrrazole. The sequence follows a different pathway in the case of enones, with the pyrrazole in this case losing nitrogen so as to leave behind a new methyl group on the double bond. Thus, the dipolar addition of diazomethane to enone (**39-3**) leads to the pyrrazole (**39-5**); that intermediate loses nitrogen on heating to give the 1 methyl enone (**39-6**), **methenolone** [39].

The 17-methlyl analogue (**40-1**) of unsaturated ketone (**39-3**) also provides entry to a compound in which the A ring is converted to a heterocycle. The fact that this compound shows full androgenic and anabolic activities demonstrates the bioisosterism of methylene and oxygen in this series. Oxidation of the 2-enone in (**40-1**) with lead tetraacetate may proceed through the initial formation of a 1,2,3 tricarbonyl compound; this undergoes ring scision and eventual loss of carbon 2 to give acid-aldehyde (**40-2**), which is in equilibrium with the lactol form (**40-3**). Reduction with sodium borohydride leads to the lactone (**40-4**) **oxandrolone** [40].
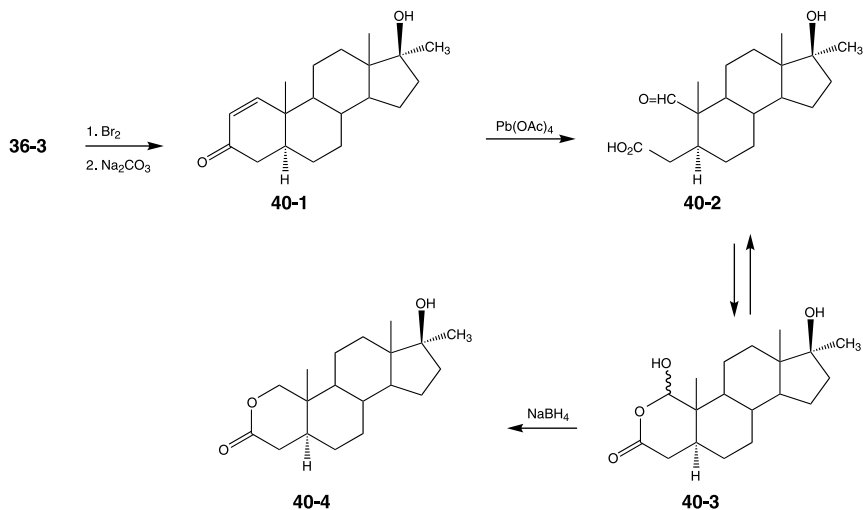
The route used to prepare the unsaturated 2 methyl androgen **stenbolone** provides yet a further illustration of the propensity for the formation of enolates at the 2 position. Thus reaction of dihydrotestosterone acetate (**41-1**) with formaldehyde and dimethylamine gives the Mannich product (**41-2**). Hydrogenolysis of that product gives the 2 methyl derivative (**41-3**); the relatively elevated temperature used for this last reaction suggests that the reaction may proceed via the methylene product

from the elimination of dimethylamine. Bromination of the ketone leads to the 2-bromo derivative (**41-4**). Dehydrobromination by means of lithium carbonate in dimethyl formamide (DMF) affords the androgen **stenbolone acetate** (**41-5**) [41].
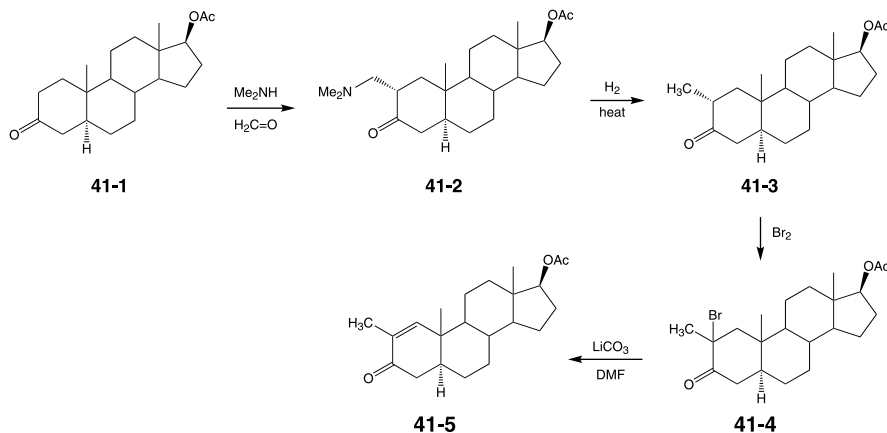
The crucial importance of the presence of oxygen at the 11 position for adrenocorticoids activity, which is discussed in greater detail in Chapter 5, led to the development of methods for introducing that substituent by microbiological methods. Thus, fermentation of progesterone with soil organisms serves to oxidize the 11 position. Some of those same organisms were found to also hydroxylate simpler steroid substrates. Thus fermentation of andostene-3,17-dione (**42-1**) obtained by Oppenauer oxidation of dehydroepiandrosterone affords the corresponding 11α hydroxyl derivative (**42-2**). Oxidation by means of Jones' reagent leads to the 3,11,17-triketone (**42-3**). The difference in reactivity of carbonyl groups at the 3 and 17 positions attributable to the greater steric bulk near the 17 ketone have played a major role in the design of several of the syntheses discussed so far. Ketones at the 11 position are so much less reactive than those at 17 that they are virtually inert to addition reactions. This lack of reactivity is due largely to the shielding effect of the two angular methyl groups, each of which bears a 1,3 diaxial relation to the carbonyl. Much of the work involved in steroid synthesis consists in taking advantage of these differences by juggling protecting groups so as to direct the reactions to the desired sites. Thus, reaction of triketone (**42-3**), also known as adrenosterone, with pyrrolidine occurs selectively at the 3 position to give the enamine (**42-4**). Condensation of that with methylmagnesium bromide followed by hydrolysis of the enamine results in the formation of the 17 methyl carbinol (**42-5**); the 11 ketone is, as expected, totally inert under the reaction conditions. The potentiating effect of fluorine, particularly at the 9α position, on biological activity was first observed in the corticoids and will be discussed in more detail in Chapter 5. Inclusion of that group starting from 11 oxygenated compounds involves a fairly standard set of transforms; the key starting intermediate usually possesses an 11β hydroxyl group. Conversion of (**42-5**) to the alcohol requires that the 3 ketone first be protected. The enamine at 3, lost during

workup, is restored by reaction with pyrrolidine; exposure to lithium aluminum hydride leads to one of the few reactions that affect carbonyl groups at position 11. Thus reduction with lithium aluminum hydride yields the 11β alcohol 179 after removal of the eneamine.
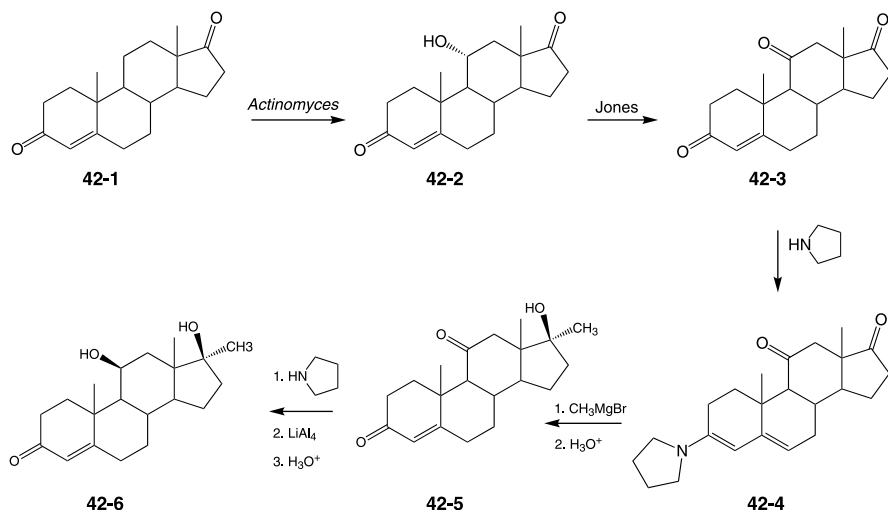
The hydroxyl in (**42-6**) is then acylated with *p*-toluenesulfonyl chloride; exposure of this to a base leads to elimination to form the 9,11 olefin (**43-1**). It should be noted that the hydroxyl group in the first-obtained fermentation product is equatorial and would eliminate only with great difficulty as it lacks a *transoid* proton at the adjacent position. Reaction of (**43-1**) with *N*-bromosuccinimide in an aqueous base leads to the addition of the elements of hypobromous acid. The stereochemistry of the reaction

Bromonium ion   Oxironium ion
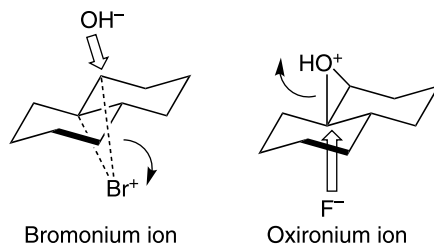
is, in all probability, determined by the initial formation of a bromonium derivative on the more open α face; diaxial opening by hydroxide leads to the bromohydrin (**43-2**). Reaction of this with a base results in the internal displacement of bromine by alkoxide to give the β epoxide (**43-3**). That compound is then allowed to react with hydrogen fluoride in THF. A diaxial opening of the intermediate oxiranium ion by fluoride anion completes the construction of the 9α-fluoro-11β-hydroxy moiety. There is thus obtained the potent androgenic agent **fluoxymestrone** (**43-4**) [42].

42-6   1. TsCl
           2. Et3N

43-1

HOBr

(NBS/OH⁻)

43-2

NaOH

43-3

HF

THF

42-4
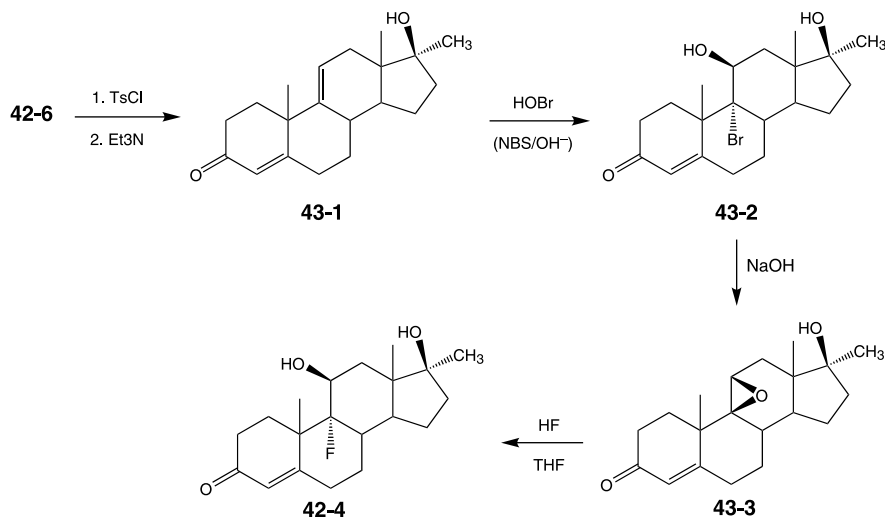
4.5.3. Antiandrogens

A group of clinically effective antiandrogens are derived from androstanes that include a carboxylic acid at position 17. The first agent in the series to show clinical activity, **finasteride** (**45-3**), involves some further significant structural changes from androgens. Similar deep-seated structural changes are seen in between progesterone and the antagonist mifepristone (**28-3**). The first step in the synthesis consists of the oxidation of the acetyl side chain in progesterone (**12-1**) to a carboxylic acid (**44-1**), as, for example, by some modification of the haloform reaction. Oxidation of the enone function in ring A with a combination of potassium permanganate and sodium periodate leads to the keto-acid (**44-2**) in which carbon 4 has been excised. The reaction can be rationalized by assuming that permanganate first

12-1   [O]   **44-1**   KMnO₄ / NaIO₄   **44-2**

NH₃/H₂

44-3

44-4   Me₃SiCl   **44-5**
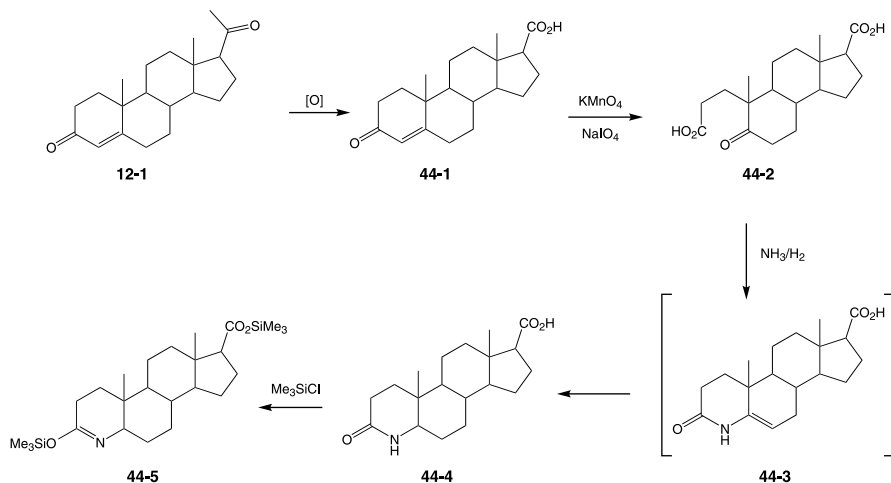
hydroxylates the double bond; cleavage of the resulting glycol by periodate will then open the ring. Further reaction then takes the 3 and 5 carbon atoms to their fully oxidized states. Reductive amination of the keto-acid with ammonia results in the formation of lactam (**44-4**). Reduction of the hypothetical initially formed 5 imino group from the more open α face will give the β amino group and consequent maintenance of steroid stereochemistry. The lactam group is then converted to its iminoether by treatment with trimethylsilyl chloride in the presence of imidazole; the carboxylic acid is transformed to its silyl ester (**44-5**) under the reaction conditions.

DDQ, 2,3-dicyano-5,6-dichlorobenzoquinone, is a much more powerful oxidizing agent than its tetrachloro analogue; the use of the latter for introducing an additional double bond at the 6,7 positions in 3-keto-4-enes has been described previously. The use of DDQ for introducing an olefin in the 1 position of 3-keto-4-enes will often be seen in the discussion of corticoids in Chapter 5. Treatment of lactam silyl enol ether (**44-5**) with DDQ introduces unsaturation at the 1 position in this compound as well (**45-1**). The silyl protecting groups are then removed with fluoride ion to give the lactam acid (**45-2**). The reduced reactivity of the carboxylic acid at the 17 position due to steric hindrance necessitates that it first be converted to an activated intermediate; reaction with carbonyl dimidazole (CDI) gives the corresponding imidazolide. Condensation of that with *tertiary*-butylamine affords the amide and thus **finasteride** (**45-3**) [43,44].
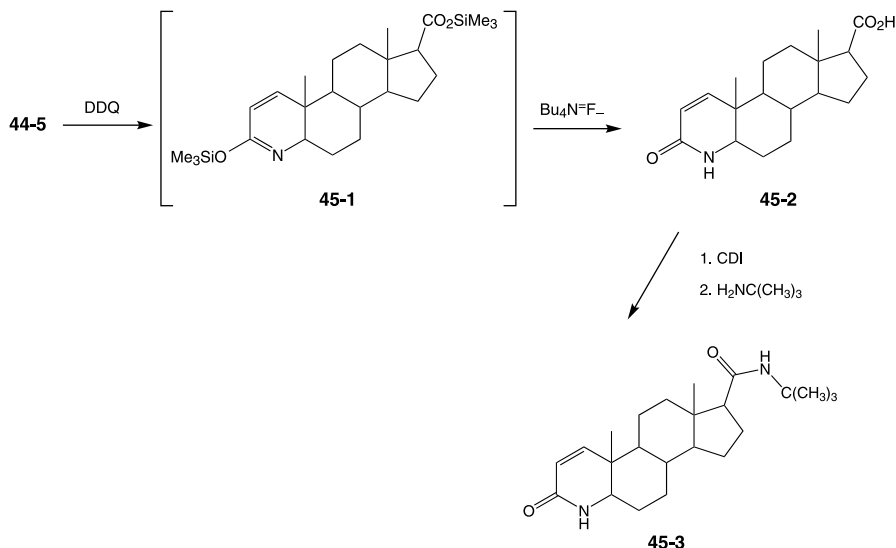
The order in which the steps are performed is quite flexible. The synthesis of the antiandrogen **dutasteride** thus starts with the construction of the side chain at 17. The reaction of acid (**44-1**) with the aniline (**46-1**) poceeds to afford the amide (**46-2**). Ring A of the steroid is then opened to the corresponding keto-acid (**46-3**) with a concomitant loss of carbon 4 by means of the permanganate–periodate combination. Reductive alkylation with ammonia then affords the saturated lactam (**46-4**).

Treatment of this last intermediate with DDQ leads to the dehydrogenation of the lactam ring to form the 1-dehydro derivative **dutasteride** (**46-5**) [45].
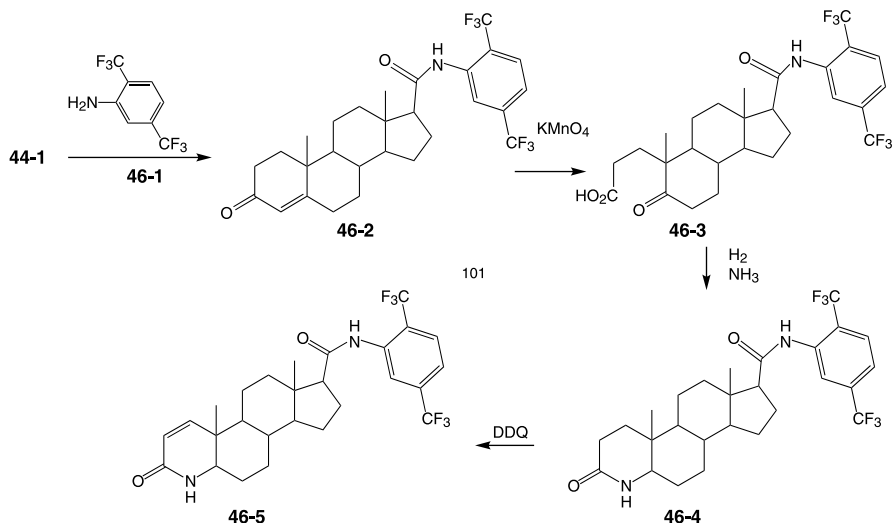
Antiandrogenic activity is retained in a related compound that lacks the unsaturation in ring A and in which in addition contains a methylated ring nitrogen. Formation of the side chain also starts the synthesis of the androgen antagonist **turosteride** (**47-3**). Reaction of the key 17-carboxylic (**44-1**) with diisopropylcarbodiimide with the acid leads to the formation of the urea side chain (**47-1**). Ring A is then opened as above to the keto-acid (**47-2**) with a loss of carbon atom at 4. Reductive amination, in this case with methylamine, leads directly to the lactam (**47-3**) [46].
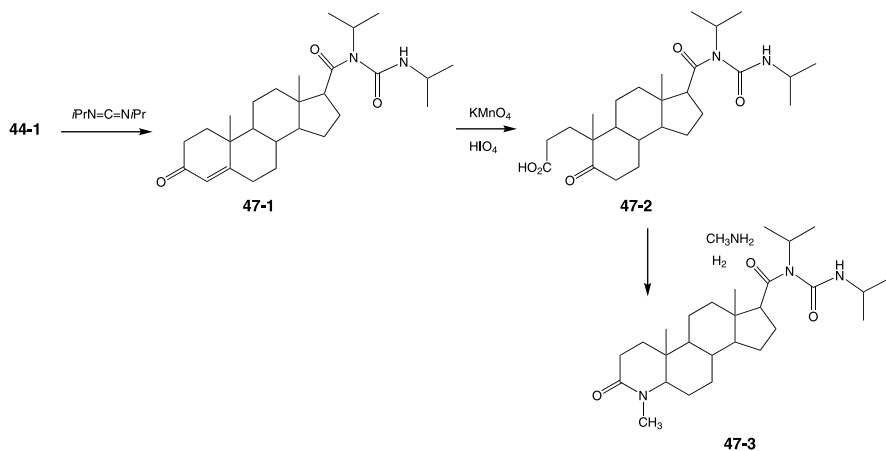
An analogue in which a carboxylic acid attached to the 3 position takes the place of the polar pyridone ring in the previous examples also exhibits antiandrogenic activity. The synthesis starts by reaction of the intermediate (**44-1**) common to the preceding antiandrogens with phosphorus tribromide. This reagent converts the

ketone at 3 to its enol bromide and the carboxyl to its acid bromide. A mild base hydrolyzes the latter back to the free acid (**48-1**). Treatment of the acid chloride formed by reaction with oxalyl chloride with *tertiary*-butylamine then gives the corresponding amide (**48-2**). An indirect process is then used to produce the intermediate 3-lithio reagant. Thus, reaction of the intermediate (**48-2**) with ethylmagnesium chloride exchanges the halide at 3 to form the 3-organomagesium reagent and ethyl chloride. Addition of butyl lithium to the reaction mixture then leads to the corresponding lithio derivative (**48-3**). Reaction with carbon dioxide leads to the carbonation of the 3 position. On workup there is thus obtained the carboxylic acid **epristeride** (**48-4**) [47].
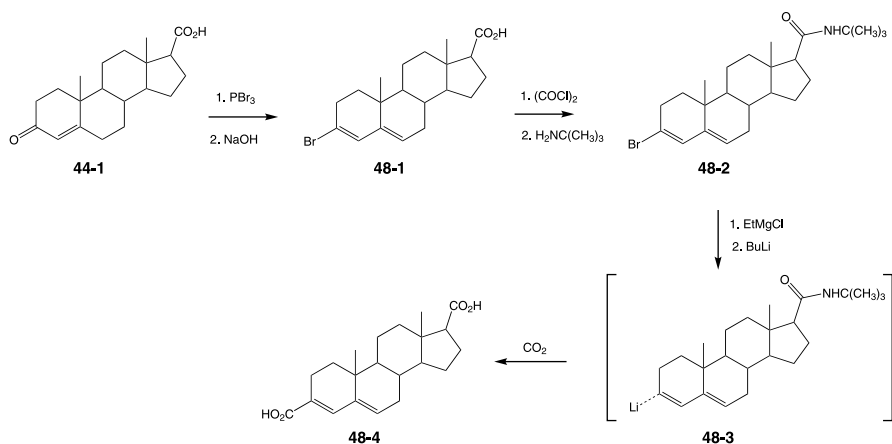
4.5.4. Aldosterone Antagonists

By far the major number of steroids isolated from extracts of the adrenal cortex consists of the so-called corticosteroids. These compounds, which include cortisone and hydrocortisone, are discussed in detail in Chapter 5. Though these compounds have marked effects on mineral transport and balance, further research indicated that most of the activity of adrenal extracts on these parameters was in fact due to a so-called amorphous fraction. The purified compound responsible for that activity, named aldosterone, was the last of the cortical steroids to be isolated and purified. The complex structure of this unusual steroid, which is oxygenated at both the 11 position and on the angular methyl group at the 13 position, delayed structural determination until well into the 1940s. It has since been established that the compound plays a key role in the renin-angiotensin system that regulates body fluid volume, sodium and potassium retention or excretion, and thus ultimately blood pressure. The adventitiously discovered aldosterone antagonists are quite effective diuretic agents. They act by opposing agonist-mediated fluid and sodium retention; they are of particular interest because they do not cause the lowering of serum potassium levels noted with the sulfonamide or thiazide diuretics. The aldosterone antagonists exert antihypertensive activity by a mechanism thought to be analogous to that of the thiazides or sulfonmades. They were used quite extensively for the treatment of high blood pressure before the emergence of more effective and better-tolerated drugs.

keto form   hemiacetal form

Aldosterone
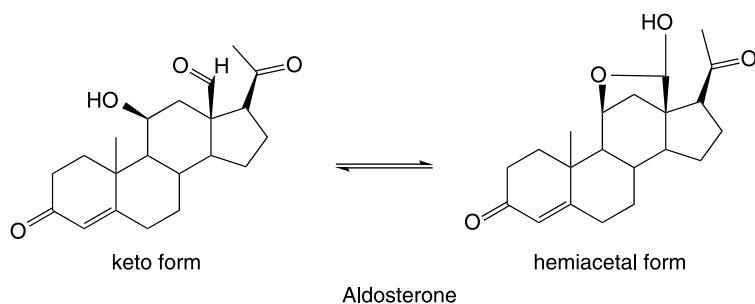
The diuretic activity of this structural class, it is believed, was first noted with the simplest member of the series (**50-5**) in the course of a wide-ranging screening program. Preparation of this compound starts with the condensation of dehydroepiandrosterone (**34-4**) with lithium acetylide to give the intermediate (**50-1**), which displays the usual preference for addition to the α face. Reaction of that with excess methylmagnesium iodide leads to the formation of magnesium salts at both the alcohols and, most importantly, at the acetylene terminus. Reaction of the salt with carbon dioxide *in situ* leads to carbonation at that position; the carboxylic acid (**50-2**) is obtained on workup. The catalytic hydrogenation over palladium then selectively reduces the triple bond (**50-3**). Treatment with acid then forms the spirocyclic lactone to give (**50-4**). Oppenauer oxidation of the hydroxyl group at 3 gives the 4-ene-3-one and completes the synthesis of (**50-5**).
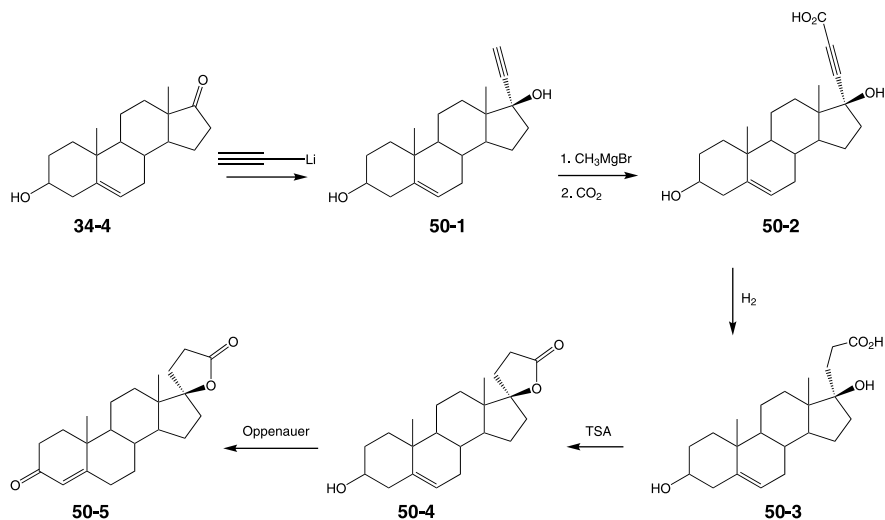
The search for compounds that had improved oral activity led initially to the 7α-thioacetyl derivative (**51-2**) [48]. Dehydrogenation of the enone function in (**50-5**) using the now-familiar quinone, chloranil, leads to the dienone (**51-1**). This undergoes 1,6 conjugate addition on treatment with the sodium salt from thioacetic acid to give the 7α derivative (**51-2**); this compound, under the name **spironolactone**, was the first clinical aldosterone antagonist. Studies on the metabolic disposition of

51-2

51-3
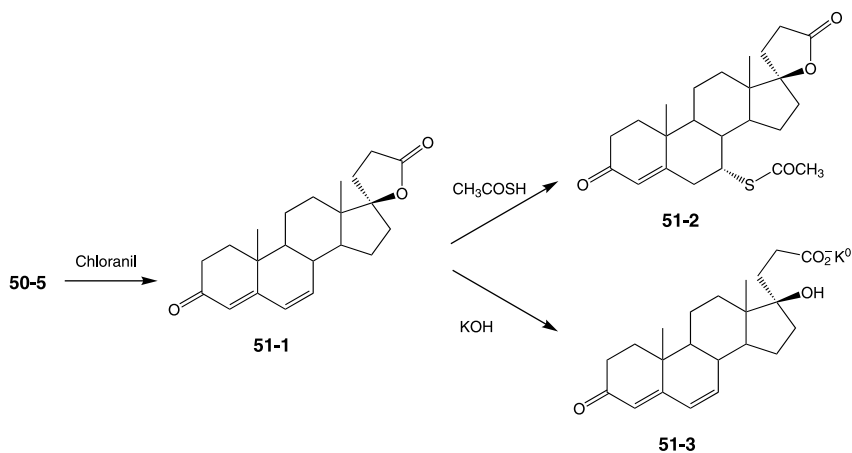
that drug revealed that the lactone not unexpectedly opened *in vivo*; the fact that the thioacetyl was eliminated as well was not anticipated. The finding that the metabolite showed full clinical activity led to its use as a drug. This compound, **canrenoate potassium** (**51-3**), is prepared by a simple ring opening of the lactone with potassium hydroxide.

A reagent more commonly used for converting carbonyl groups to homologous epoxides interestingly converts the terminal olefin of a dienone to cyclopropane. Thus reaction of dienone (**51-1**) (**canrenone**) with the yilide from trimethylsulfonium iodide can be envisioned to afford the betaine (**52-1**) as an intermediate. Return of the negative charge results in the displacement of neutral dimethyl sulfide and the consequent formation of a cyclopropyl ring. The product, **prorenone** (**52-3**), is used as its lactone ring opened potassium salt **prorenoate potassium** (**52-3**) [49].

52-1

52-3   **52-2**
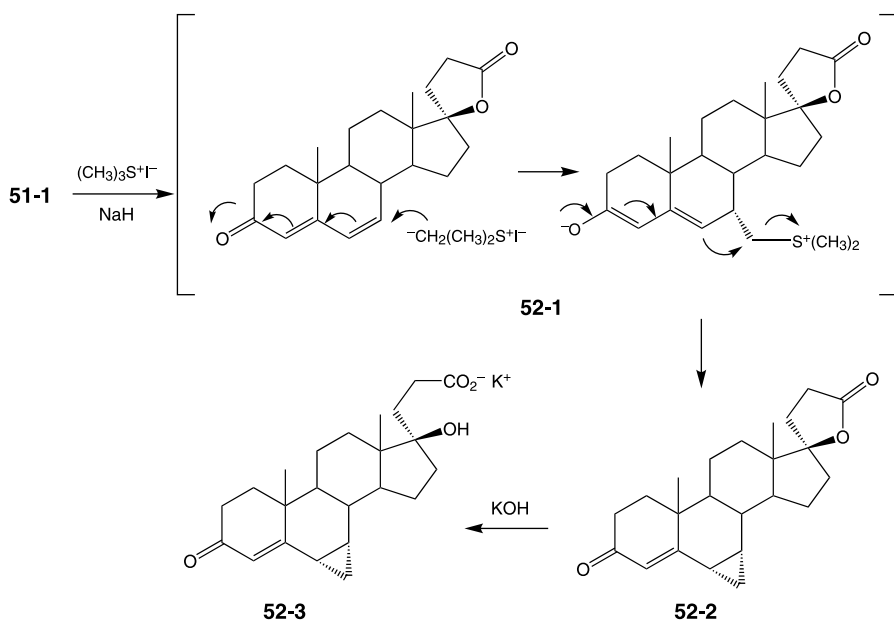
The **spironolactone** analogue in which the thioacetyl group is replaced by a carboxylate ester retains the activity of the parent, indicating that metabolism to a **canrenone**-like product is not an absolute requirement. The actual chemical manipulations involved in the transformation, addition of cyanide, hydrolysis, and finally treatment with sodium methoxide belie the complexity of the actual chemistry. The product isolated from the first step in fact consists of the bridged bicyclic imine (**53-2**). The initial 1,6 addition product to dienone (**51-1**) apparently first forms a neutral 7-cyano 4-ene-3-one. That product then undergoes addition of a second mole of cyanide to give (**53-1**). Addition of that second cyanide to the β face may be due to the hindrance from the cyano group at the 7 position; this also results in the AB ring junction assuming the *cis* decalin conformation, in effect forcing the 4 position into close proximity to the 7α nitrile. This closes in the basic reaction medium to give the observed product (**53-2**). Hydrolysis of the product with mild acid leads to the ketone (**53-3**).
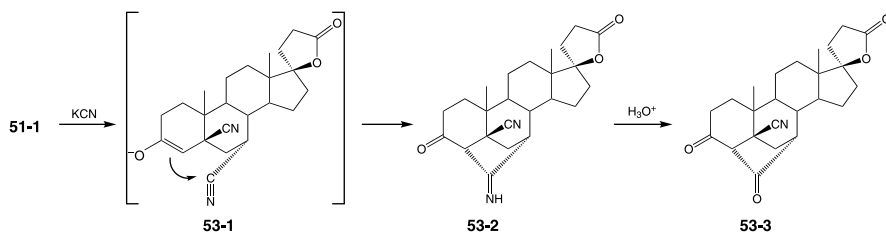
The final step involves the reaction of (**53-3**) with sodium methoxide. The overall transformations can be envisaged by assuming that the methoxide first adds to bridge
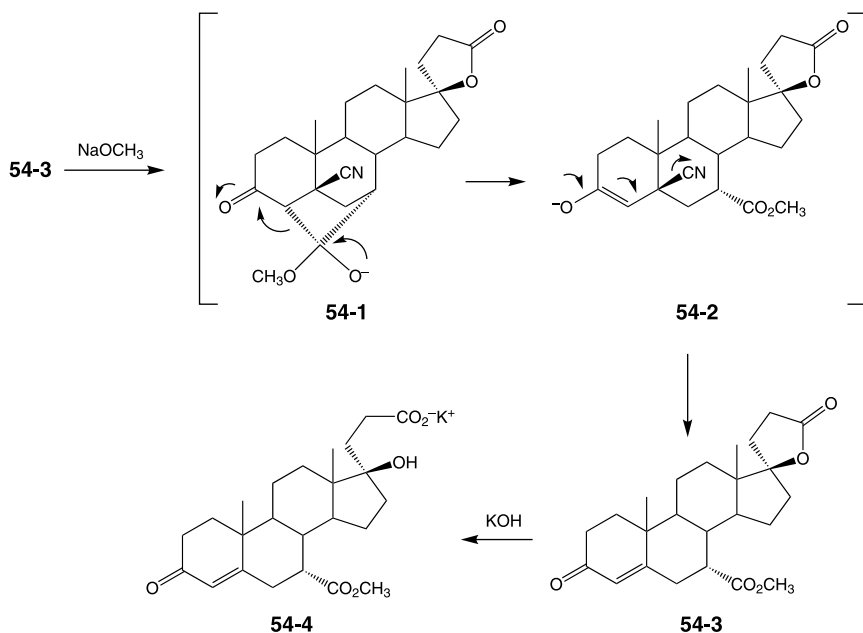
ketone to give an intermediate such as (**54-1**). Steric strain, albeit small, would drive scission of the bridging ring to give the enolate (**54-2**). This compound is in fact equivalent to the initial intermediate from the conjugate addition to the 4-ene-3-one; simple reversal gives the neutral product (**54-3**) and thus **mexrenone** [50]. This compound, too, is used as the potassium salt of the ring opened form, in this case **mexrenoate potassium** (**54-4**).

Potency is significantly increased by incorporation of oxygen at the 11 position. At first sight this might be attributed to the fact that aldosterone itself has an 11 hydroxyl group; the oxygen atom in **epleronone** (**55-5**), however, occupies the opposite face of the steroid from that in aldosterone. The 9,11 dehydro starting material (**55-1**) is in all likelihood derived from one of the 11 oxygenated compounds involved in the syntheses of corticoids described in Chapter 5. Reaction of this intermediate with cyanide in the presence of triethylaluminum in contrast to the preceding example proceeds in customary fashion to afford the product from 1,6 addition to the dienone (**55-2**). A roundabout scheme is used to avoid the harsh conditions involved in the hydrolysis of nitriles. The cyano group is thus first reduced to the corresponding imine with diisobutyl aluminum hydride. This affords the aldehyde (**55-3**) on hydrolytic workup. The aldehyde is then oxidized to carboxylic acid and that intermediate converted to the ester (**55-4**) by means of diazomethane. The highly sterically hindered 9,11 unsaturation is then oxidized with hydrogen peroxide in acetonitrile. The α-stereochemistry of the product may be due to the participation of the nearby ester group. There is thus obtained the aldosterone antagonist **eplerenone** (**55-5**) [51].
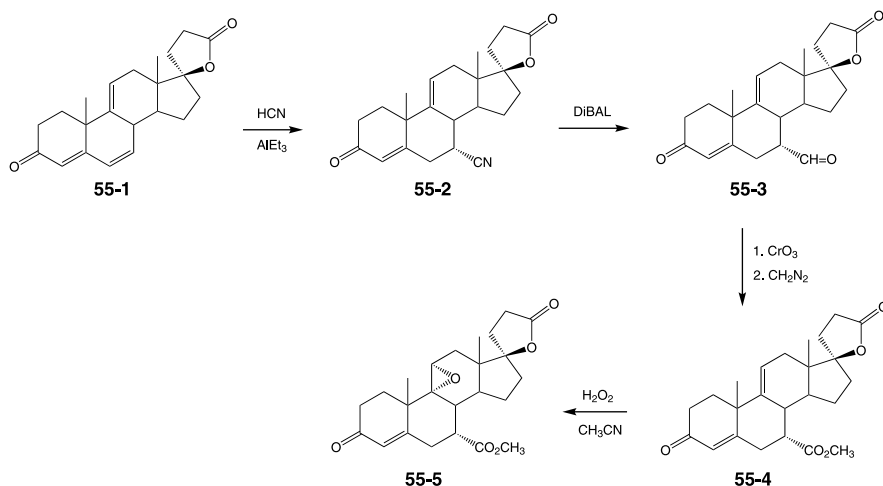
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CHAPTER 5

STEROIDS; PART 2: COMPOUNDS RELATED TO PROGESTERONE, CORTISONE, AND CHOLESTEROL

5.1. INTRODUCTION

The classical progestins as well as the corticosteroids are based on a steroid nucleus that incorporates a two-carbon side chain at the 17 position that often includes a carbonyl group at position 21. The hypothetical parent hydrocarbon has been assigned the name *pregnane* for purposes of nomenclature. While two classes of compounds, progestins and corticoids, share common biosynthetic pathways, their biological activities differ markedly.
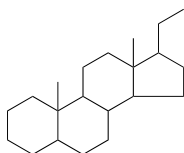
5.2. PROGESTINS

Progesterone ranks with estradiol as one of the key hormones that controls the reproductive cycle in the mammalian female. Progesterone, synthesized by a structure on the ovary that forms immediately after ovulation known as the corpus luteum, inhibits subsequent ovulation until the next cycle. Increased levels of progesterone are essential in

permitting implantation of fertilized ova as well as providing a hospitable intrauterine milieu for the developing fetus. The most important application of the progestational 19-nor steroids (gonanes), discussed in Chapter 4, involves their use in oral contraceptives. The progestational agents more directly related structurally to progesterone itself are used largely as drugs for treating various conditions related to progesterone deficiency. Several of these, however, had at one time been included as the progestational component in oral contraceptives. Their discontinuation was probably due more to marketing than medical reasons, since they had been preceded by their 9-nor counterparts by some years. Progesterone itself, it will be recalled, is poorly available on oral administration and is readily metabolized to inactive derivatives. Most of the analogues of the hormone that retain the full carbon skeleton, sometimes called C-19 steroids, were aimed at overcoming these shortcomings.

Potency and oral activity of progestins in the pregnane class are enhanced by the presence of additional substitution at various positions. The presence of acyloxy groups at the 17α position has proven a particularly important modification and is present in virtually all modified progestins. One of the original preparations for the prototype compounds starts by epoxidation of pregn-17-enolone obtained from saponification of the acetate (**2-1**). The use of a peracid would preferentially lead to a reaction at the 5,6 olefin because of its higher electron density over that at the 16,17 position. The initial step in the reaction with basic hydrogen peroxide is more akin to a Michael addition than a classic epoxidation; the reaction with that reagent thus occurs selectively at the conjugated double bond at 16,17 to give (**2-2**) as the observed product. Exposure to hydrogen bromide leads to the bromohydrin (**2-3**)
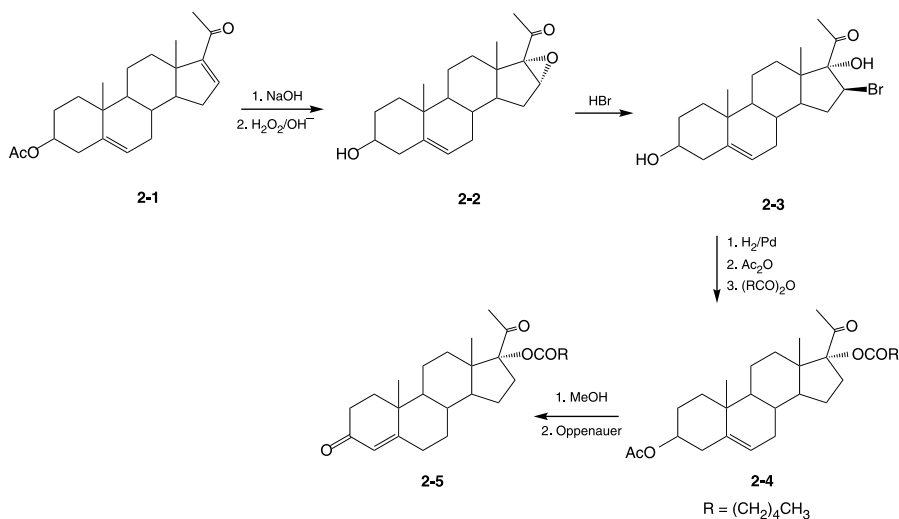
from a pseudo-diaxial opening. Catalytic hydrogenation over palladium in the presence of ammonium acetate interestingly preferentially reduces the bromine over the remaining olefin. Acetylation under standard conditions selectively acylates the hydroxyl at position 3 over the very hindered, and tertiary, 17 alcohol [1]. The 17

alcohol can, however, be acylated under forcing conditions; thus reaction with hexanoic (caproic) anhydride in the presence of *para*-toluenesulfonic acid leads to the diester (**2-4**). Methanolysis occurs selectively at the 3 position. The resulting alcohol is then oxidized with aluminum isopropoxide in the presence of cyclohexanone to give **hydroxyprogesterone caproate** (**2-5**). This very lipophilic ester is quite soluble in vegetable oils and is thus used for injection as depots that provide long-term progestin blood levels.

The addition of a methyl group at the 6α position enhances potency as it does in the case of the androgens. Oppenauer oxidation of 17-hydroxypregnolone from debromination of bromohydrin (**2-3**) leads in a straightforward manner to the formation of the conjugated ketone and thus 17α-hydroxyprogesterone (**3-1**). Reaction of that compound with an excess of ethylene glycol in the presence of acid gives the corresponding *bis*-acetal (**3-2**). The very generally observed shift of the olefin to the 5,6 position on forming acetals of conjugated 3-one-4-enes has the fortunate consequence of providing a reaction center at the 6 position; the reasons for this bond reorganization are not immediately obvious. Reaction of the product with *meta*-chloroperbenzoic acid leads to the formation of the α epoxide (**3-3**), which results from reaction at the more open face of the molecule. Condensation of that with methyl Grignard reagent leads to the product (**3-4**) from a diaxial opening of the oxirane.
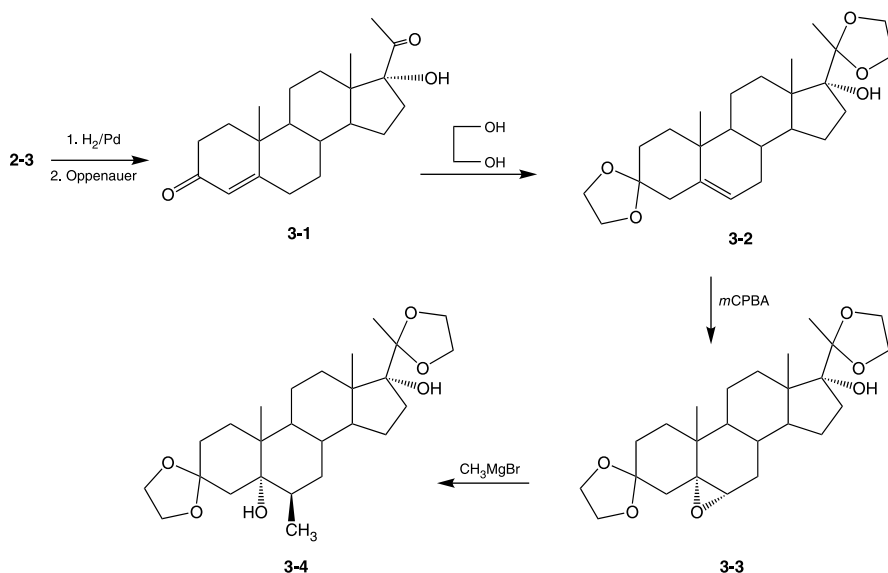
The acetals groups are then removed by hydrolysis of the compound in a mixture of acetone and dilute mineral acid to give the β-hydroxy ketone (**4-1**). This undergoes reverse Michael addition of water on treatment with a base to give the conjugated ketone (**4-2**). Treatment with a base causes a methyl group at 6 to epimerize to the more stable α configuration. Acetylation with acetic anhydride under forcing

conditions affords **medroxyprogesterone acetate** (**4-3**) [2], a quite potent orally active progestin. A far more important use for the drug hinges on its solubility in lipids; the drug can thus be injected to form depots that provide long-term levels of progestin. The drug is sufficiently potent so that these levels provide sufficient progestational activity to prevent ovulation and in effect provide an injectable contraceptive. This drug, Depo-Provera®, may incidentally have set a record in that it took close to two decades from application to final approval for that indication by the U.S. FDA; noncontraceptive uses, on the other hand, were approved in the early 1960s. Reaction of (**4-3**) with chloranil leads to the introduction of an additional double bond at the 6,7 position to afford the potent progestin **megestrol acetate** (**4-4**) [3]. This compound has found some use in the treatment of breast cancer.
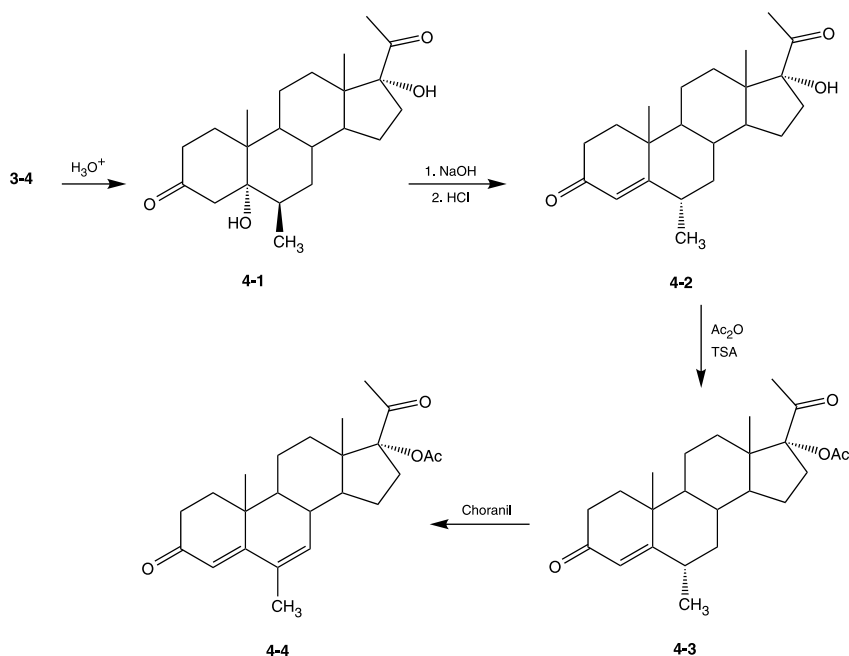
Biological activity is often retained when a methyl group is replaced by chlorine, suggesting that steric factors outweigh electronic considerations in those cases. The synthesis of 6-chloro progestins follows much the same route as that used for the methylated counterparts. The scheme begins with the acetylation of 17α-hydroxyprogesterone (**3-1**), under forcing conditions. The 6,7 double bond is then introduced by dehydrogenation with chloranil to give dienone (**5-1**). Reaction of that compound with basic hydrogen peroxide starts with an initial conjugate addition of the hydroperoxy anion to the terminus of the conjugated system; the end product is the 6α,7α epoxide (**5-2**). Reaction with anhydrous hydrogen chloride proceeds via the normal diaxial opening to afford the 6-chloro-7-hydroxy derivative; this compound dehydrates under reaction conditions to afford the chlorinated diene **chlormadinone acetate** (**5-3**) [4]. The high potency and good bioavailability of this drug led to its use

as a contraceptive. It is of note that it showed reasonable efficacy in the absence of co-administered estrogens. In contrast to the 19-nor progestins, metabolic conversion to an estrogen is not a consideration with this compound. The poor control of the menstrual cycle that accompanied its use was sufficiently unattractive to lead to its discontinuation as a contraceptive. It is, however, still used to regulate estrus in some domestic animals. Dehydrogenation of that product with selenium dioxide leads to the introduction of the double bond at the 1 position to afford the highly potent progestin 1,4,6-trienone (**5-4**), **delmadinone acetate** [5].
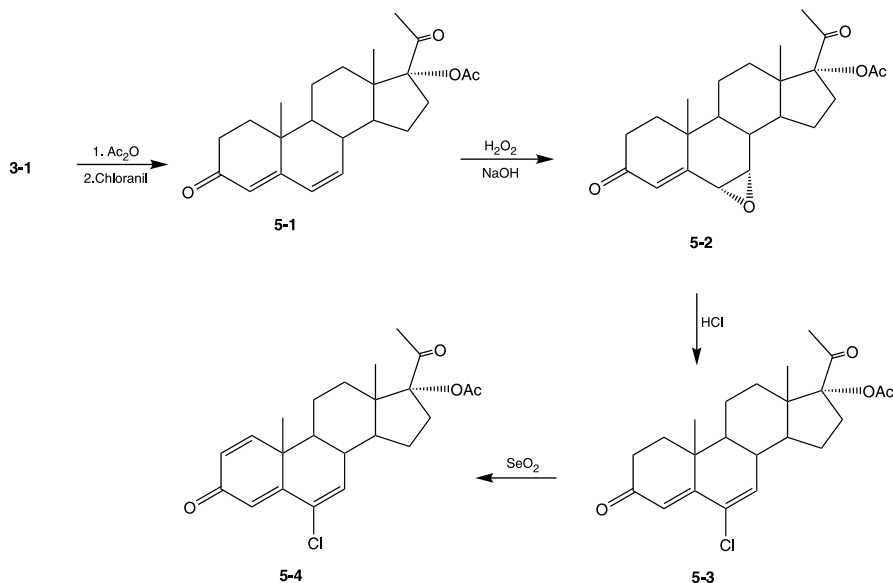
The observation that the effect of potentiating groups is additive is one of the hallmarks of the medicinal chemistry of steroids. This phenomenon, illustrated time and again in the area of corticosteroids, is also seen in the progestins. The drug **melengestrol acetate** (**8-4**), which includes activating alkyl groups at both the 6 and 16 positions as well as extended conjugated unsaturation, is one of the most potent progestins to have been described. One of the more interesting syntheses for this agent goes back to diosgenin (see Chapter 4) as the starting material in order to take advantage of the fact that the 21-keto-16-ene functionality is present in that molecule in protected latent form. The first step after the formation of a tosylate (**6-1**) at the 3 position involves solvolysis of that compound. These conditions lead the homoallylic tosylate to undergo a classic cyclopropylcarbynyl rearrangement, which has been discussed in detail in Chapter 1, to afford the cyclopropyl carbinol (**6-2**). It should be noted in passing that this rearrangement was in all probability first observed in the steroid series due to the ubiquity of the 3-hydroxy-5-ene functionality as well as the fact that the groups are ideally disposed sterically for the transformation. Oxidation of the alcohol with the chromium trioxide:pyridine complex leads to the 6 ketone. This is then condensed with methyl Grignard reagent to give the tertiary carbinol (**6-3**).

Solvolysis of this leads to the reverse rearrangement and restoration of the homoallyl alcohol function (**6-4**), with the net addition of a methyl group at the 6 position.
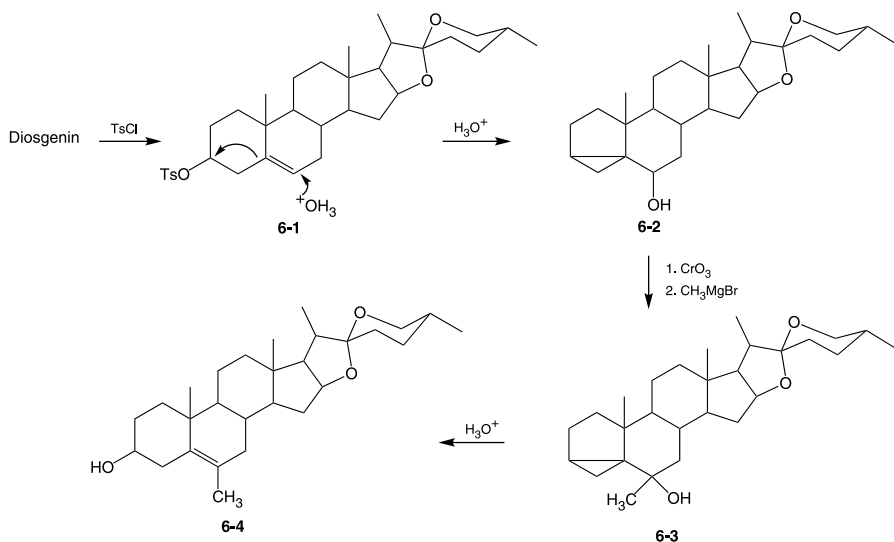
The product (**6-4**) from that sequence, which is of course simply 6-methyldiosgenin, is then subjected to a series of degradation reactions as those used for the parent compound to give the 6-methyl derivative (**7-1**) of dehydropregnenolone. Reaction of the enone function of that product with diazomethane leads to 1,3-dipolar addition and the formation of the pyrrazoline (**7-2**). That intermediate loses
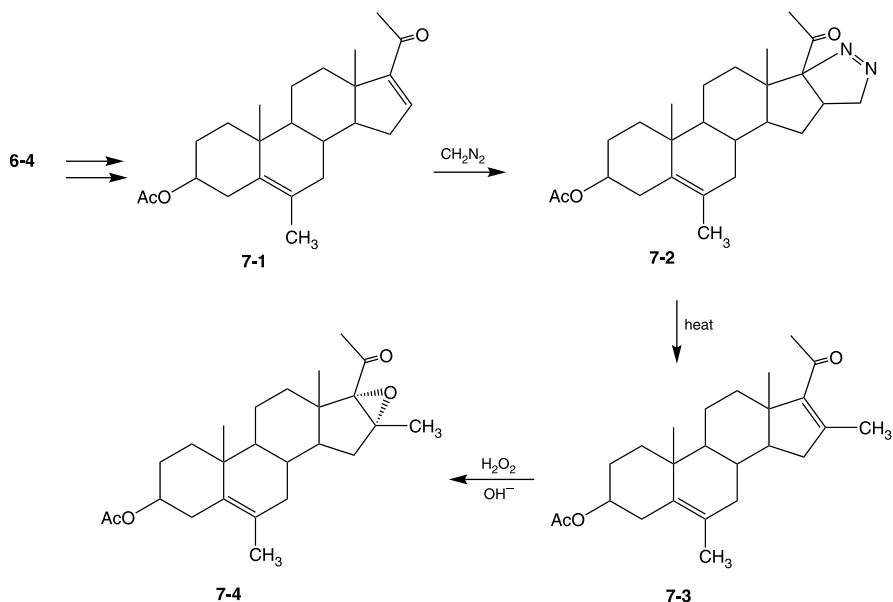
nitrogen on pyrolysis to form the 16 methyl derivative (**7-3**), in keeping with the generalization that diazomethane adducts from enones form enone-methyl derivatives instead of cyclopropanes. Treatment of the product with basic hydrogen peroxide leads to preferential formation of the epoxide (**7-4**) from the conjugated olefin at the 16 position.

The epoxyketone in (**7-4**) rearranges to an allyl alcohol when treated with acid. The reaction can be rationalized by assuming that the first step involves the protonation of epoxide oxygen as in (**8-1**). The subsequent step involves either a concerted ring opening and proton loss as shown or a stepwise opening to a carbocation followed by the loss of a proton from the methyl group. The allylic acetate in the product is then sequentially saponified and the resulting alcohol oxidized to an enone to give (**8-3**). Dehydrogenation by means of chloranil completes the synthesis of **melengesterol acetate** (**8-4**) [6].
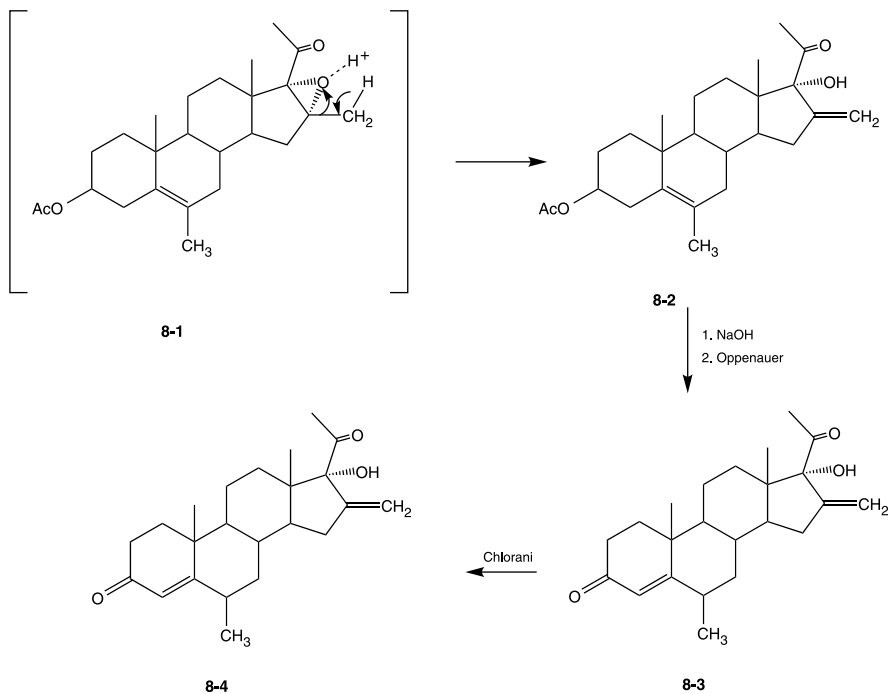
The analogue of **megestrol acetate** in which a methyl group replaces the acetoxy function at the 17α position displays good oral progestational activity, suggesting that mere bulk is required at that position. The first step in the preparation of that analogue involves reaction of the 16-dehydro-6-methylpregnenolone acetate (**7-1**) with lithium in liquid ammonia in a modified Birch reduction to give the anion (**9-1**) as an intermediate. Quenching with methyl iodide results in the alkylation of the anion at the 17 position; the usual steric course, that is, the approach of the reagent from the more open α face, is followed to give (**9-2**) as the product. The basic conditions result in the hydrolysis of the acetate at the 3 position. Oxidation of this last intermediate

under Oppenauer conditions leads to the conjugated enone; dehydrogenation of that product with chloranil establishes the dienone function. There is thus obtained **medrogestone (9-3)** [7].
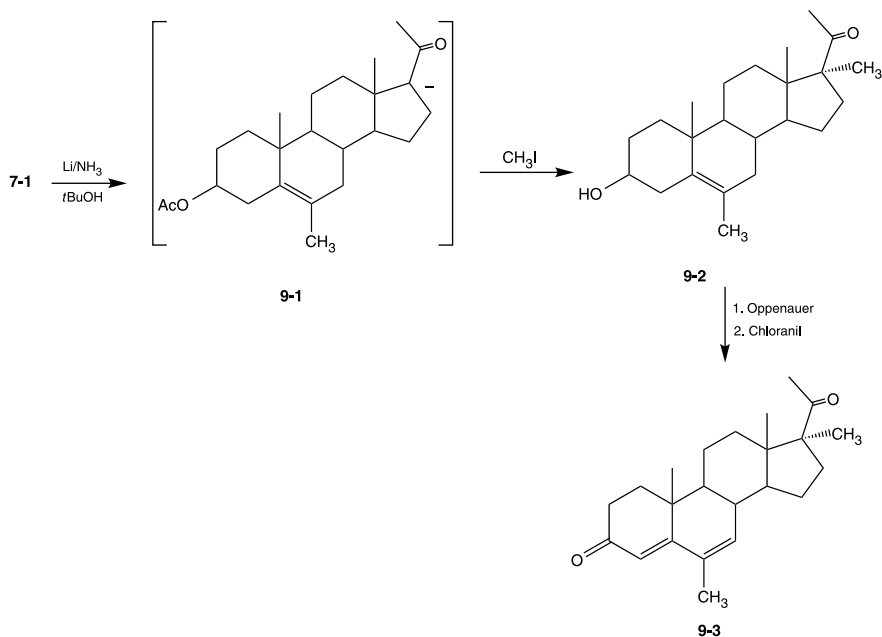
It is generally accepted that all steroids, be they endogenous compounds or products of semi-synthesis, act by interacting with specific receptors. This leads to the unspoken assumption in the medicinal chemistry of steroids that the only compounds that will be biologically active are those whose configuration of the cyclopentaphenanthrene nucleus directly mimics that of naturally occurring steroid hormones. The CD ring junction in particular must have a *trans* stereochemistry that leads to a flat molecule. An apparent contradiction lies in the equivalent antiprogestational activity of **mifepristone**, which features a CD *trans* fusion and its analogue, **onapristone**, with an "unnatural" *cis* CD ring fusion and reversed stereochemistry at position 17 (see Chapter 4). A similar deviation from that assumption had been observed several decades earlier in the progestin series. The drug **didrogesterone (10-6)**, which also features a CD *cis* fusion, shows full agonist activity. The stereochemistry in this case, as with onapristone, is determined by a photochemical reaction. The starting allylic bromide (**10-1**) for that drug is obtained by bromination of pregnenolone acetate with bromohydantoin. Dehydrobromination of the product with 2,4,6-collidine gives the conjugated diene (**10-2**), which contains a functional array reminiscent of the vitamin D precursor ergosterol. Like the latter, (**10-2**) ring opens on irradiation to the presumed intermediate triene (**10-3**). Re-cyclization of that intermediate results in a product (**10-4**) with reversed configurations at both C-9 and C-10. The stereochemistry can be rationalized by noting that the transition leading to this product is free from the nonbonding interaction between the angular methyl groups

present in that which leads back to the starting material. The same argument would apply if the cleavage and ring closure went via a 9,10 diradical. Oppenauer oxidation of the product leads to the enone (**10-5**) in which only one of the double bonds migrates. Treatment of that intermediate with acid leads to the conjugated dienone and thus the progestin **didrogestone** (**10-6**) [8].
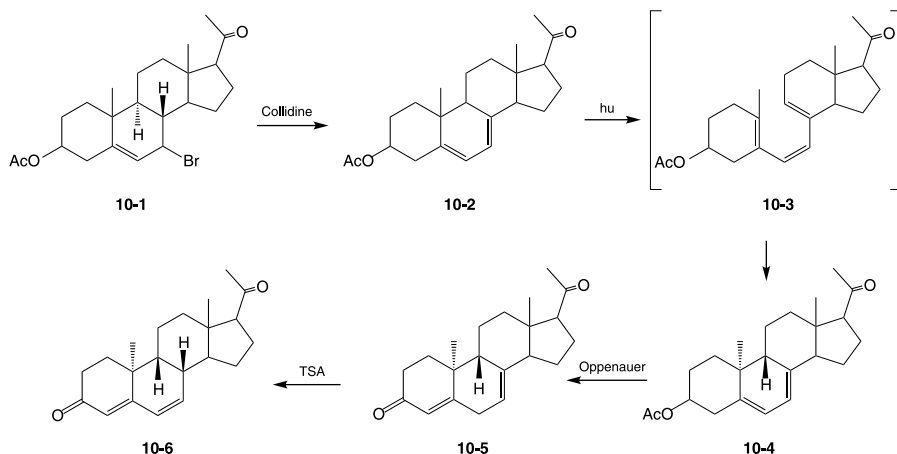
Therapeutic indications for the progestational drugs based on pregnanes described above are rather limited. This is particularly true when compared to the reduced estrane-based "nor" compounds that are used in oral contraceptives. This circumstance, combined with the availability of the half-dozen or so C-19 progestins, posed as a disincentive to further research on the synthesis of new compounds. This is reflected in the publication dates of reports on the synthesis of these compounds.

5.3. CORTICOSTEROIDS

The corticosteroids, a group of 11 oxygenated pregnanes secreted by the adrenal cortex, play a key role in the regulation of a sizeable number of homeostatic responses. It has been known since at least the mid-1920s that the pathology that resulted in experimental animal models from adrenalectomy could be reversed by the administration of extracts from the adrenal cortex. Subsequent detailed investigation established that this activity was due mainly to two closely related steroids, cortisone and cortisol. The structures of these compounds differed from the progesterone in the presence of a ketone or hydroxyl group at the 11 position and further oxidation of the side chain at the 17 position to the dihydroxyacetone stage. Interest in this class of compounds might have been restricted to use as replacements in cases of adrenal insufficiency, but for the serendipitous discovery of their profound and widespread anti-inflammatory activity. The observation that arthritis seemed to improve in the presence of elevated levels of endogenous cortisone, together with the availability of adequate amounts of the drug from synthesis, prompted clinical trials [9]. These

trials confirmed the anti-inflammatory activity of the compound, particularly when it was administered in supra-physiological doses. There followed several decades of research in many laboratories aimed at developing drugs that were more potent as well as agents that alleviated inflammation without the attendant corticosteroid activity. Though the first goal was eventually achieved, the development of analogues devoid of hormonal effects proved more elusive. This split in activity was, however, partly achieved, as will be discussed, by changing the method by which the drug is administered. The use of anti-inflammatory corticoids came to be restricted as serious side effects directly traceable to their intrinsic hormonal activity became manifest. One of those effects results in a shutdown of endogenous cortisone production by a feedback mechanism at the level of the pituitary; this accounts for the fact that any course of treatment ends with gradual diminution of the dose rather than abrupt cessation, so as to allow endogenous synthesis to resume.

It has been established that corticoids owe their antiinflammatory activity to the inhibition of phospholipase A_2, the enzyme that releases arachidonic acid from storage sites. This decreases levels of mediators from both legs of the arachidonic acid cascade (see Chapter 1). Their widespread activity is thus attributed to decreased levels of both prostaglandins and leukotrienes. The NSAIDs, it will be recalled, specifically inhibit cyclooxygenase enzymes and as a result affect only levels of prostaglandins. Many of the symptoms that accompany allergies, it has been found, are due to leukotrienes from the other arm of the cascade. Corticoids, as a result, gained a second life as anti-allergic agents. This application is revisited later in this chapter.

The rarity of steroid natural products that included an oxygen function at the 11 position combined with the chemical isolation of that position proved a stumbling block to early steroid work. Though it had been shown that the mammalian biosynthesis of cortisone from progesterone could be replicated *ex vivo* by perfusing that compound through beef adrenal slices, that procedure was not practical for the scale required for preparing synthetic intermediates. The search for a counterpart to that reaction in a prokaryotic organism was rewarded at the Upjohn Company by the finding that several molds of the *Rhizopus* family would hydroxylate progesterone to its 11-α-hydroxy derivative (**11-1**). That compound became the key to the preparation
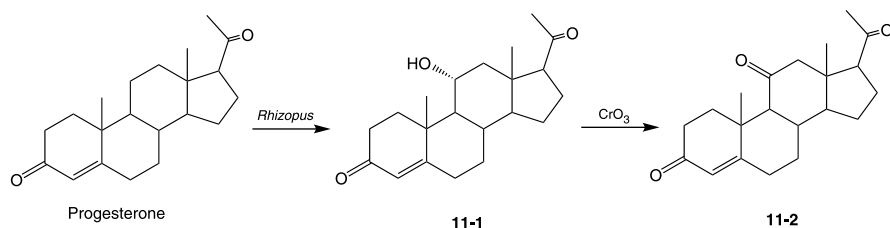
of synthetic corticoids; note, however, that the configuration of the new hydroxyl (α) is reversed from that required for corticoid activity (β). The next sequence represents one of the several methods that have been used to convert the acetyl side chain to a dihydroxy acetone. In spite of its apparent complexity this was, and may still be, one of the methods for commercial, large-scale production of bulk corticoids. The first step

consists in oxidation of the 11α alcohol to the corresponding somewhat more robust ketone (**11-2**).

In order to activate the 21 position to halogenation, it is first converted to an oxalate. Condensation of the triketone with ethyl oxalate in the presence of alkoxide proceeds preferentially at the 21 position to give (**12-2**) due to the well-known enhanced reactivity of methyl ketones. Reaction of the crude sodium enolate with bromine leads to the dibromide (**12-3**), the oxalate moiety being cleaved under the reaction conditions. The Favorskii rearrangement is then used to, in effect, oxidize the 17 position so as to provide a site for the future hydroxyl group. Thus, treatment of (**12-3**) with an excess of sodium methoxide first provides an anion at the 17 position (**12-4**). This then cyclizes to the transient cyclopropanone (**12-5**)
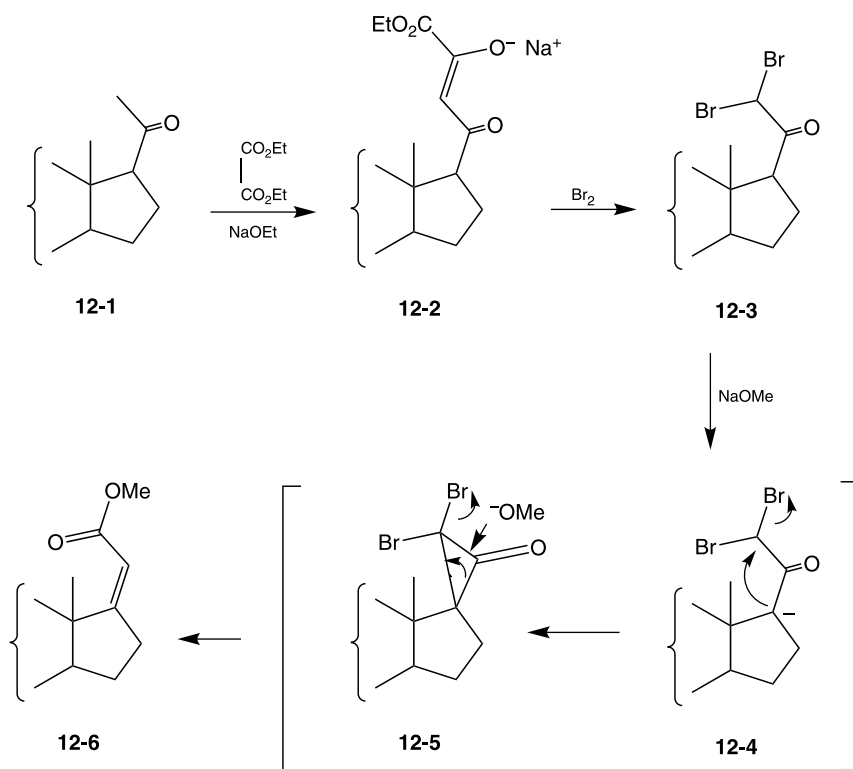
characteristic of Favorskii rearrangements. Addition of the second mole of alkoxide to the carbonyl leads to an acrylate ester (**12-6**) with a simultaneous loss of bromide. Ring opening in the opposite sense is disfavored for several reasons, including the fact that it would lead to a bulky quaternary center at the 17 position. The *cis* stereochemistry about the double bond, which has been formally demonstrated, is probably due to the stereochemistry about the spirocyclic carbonyl in (**12-5**).

The ketone group at the 3 position is then protected as its acetal (**13-2**) by reaction with ethylene glycol, the carbonyl at 11 being totally resistant to those conditions.

The enone double bond undergoes the customary shift to the 5,6 position. Treatment with lithium aluminum hydride reduces the acrylate ester at the 17 position to an allyl ether. The ketone at 11 is reduced to an alcohol in the same step; the approach of hydride from the open α side results in a hydroxyl group that has the β configuration of active corticoids. Hydrolysis of the acetal to the 4-ene-3-one followed by acetylation of the hydroxyl at 21 affords the intermediate (**13-3**), the 11β hydroxyl group being resistant to acetylating conditions. The remaining task consists in conversion of the 17,20 double bond to a keto alcohol. This is accomplished in a single step with a special combination of reagents. Osmium tetroxide is the reagent of choice for this transformation since it is well known for its ability to convert olefins to trans 1,2-diols; it is, however, quite expensive and very toxic. The reaction is thus carried out in the presence of a co-oxidant, N-methylmorpholine oxide peroxide (NMOP). This first regenerates osmium tetroxide from the initially formed cyclic
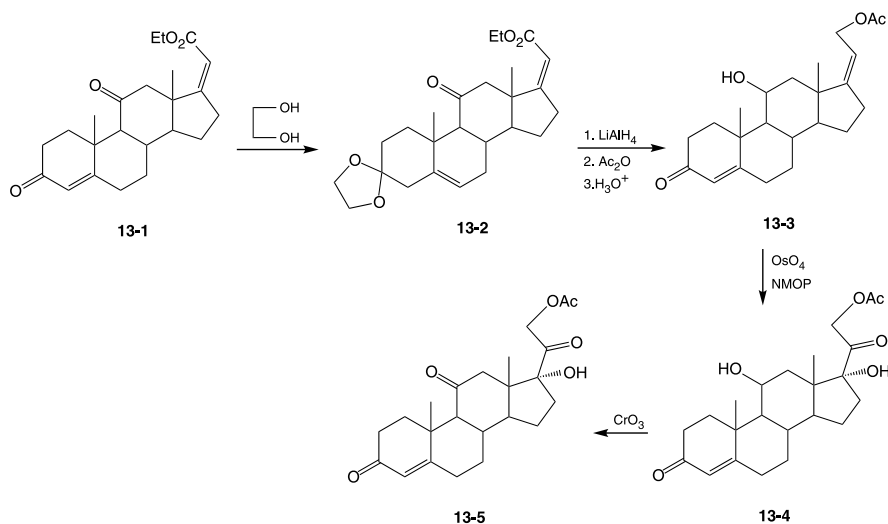
osmate ester, allowing that hydroxylating reagent to be used in catalytic amounts. NMOP is, in addition, a sufficiently strong oxidant to then convert the hydroxyl at 20 to a ketone. Thus, reaction of (**13-3**) under those conditions completes the formation of the dihydroxyacetone side chain and **hydrocortisone acetate** (**13-4**). Further oxidation of the 11 hydroxyl group with, for example, Jones' reagent gives **cortisone acetate** (**13-5**) [10].

The increase in potency observed in the progestin series by incorporation of additional unsaturation in the A ring (see **delmadinone**, (**5-4**) obtains in the corticoid series as well; the majority of commercial steroid anti-inflamatories in fact include this feature. The double bond at the 1 position may be formed by fermentation with an organism such as *Corynebacterium simplex* [11] or by reaction with selenium dioxide. **Hydrocortisone acetate** (**13-4**) yields the widely used corticoid **prednisolone acetate** (**14-1**); in the same vein, **cortisone acetate** (**13-5**) goes to **prednisone acetate** (**14-2**). Mild saponification of either of these products yields the free alcohols **prednisolone** and **prednisone**, respectively.

13-4 ⟶

13-5 ⟶

14-1   **14-2**
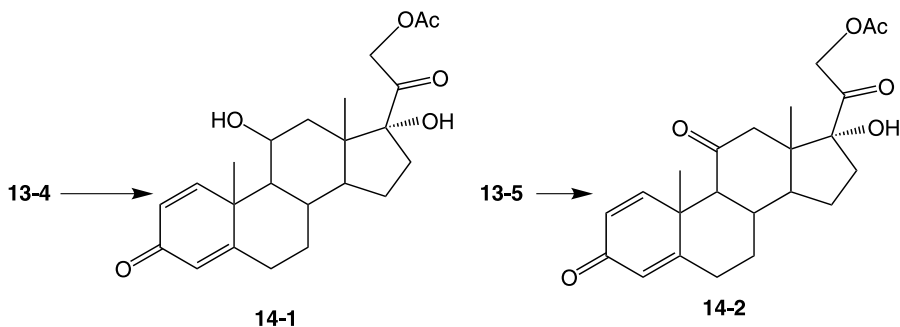
The additive effect of potentiating groups noted for progestins obtains in the corticoid series as well. While these cannot be simply summed arithmetically, cases where effects from two such groups cancel each other are very rare. Thus, substituents at the 6,9 and 16 positions generally lead to additive increases in potency. One of the first potentiating groups to be recognized is a fluorine substituent at the 9α position. The key intermediate to 9 fluorinated compounds consists of the corresponding corticoids, which have a double bond at the 9,11 position. The 9α-fluoro-11β-hydroxy moiety is then constructed by the scheme that involves the formation of a 9β-epoxide followed by its opening with the hydrogen fluoride : tetrahydrofuran complex, which is described in detail in Chapter 4 in connection with the synthesis of **fluoxymestrone**. Dehydration of hydrocortisone acetate (**13-4**) proceeds preferentially at the 11 hydroxyl

13-4 $\xrightarrow{\text{POCl}_3}$

1. HOBr
2. NaOH
3. HF/THF

15-1   **15-2**
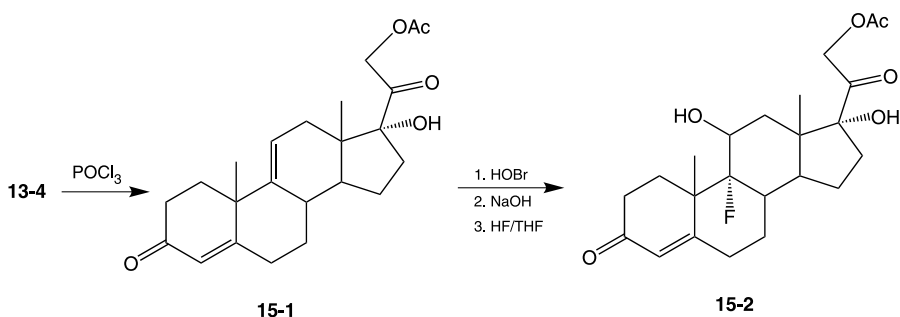
to give the diene (**15-1**); reactivity of the tertiary alcohol at the 17 position is seemingly decreased by the adjacent ketone. The diene is then subjected to the standard hydroxy-fluorination scheme, with the reaction proceeding at more electrons of the double bonds. There is thus obtained **fludrocortisone acetate** (**15-2**) [12], a compound that is close to an order of magnitude more potent than cortisol acetate in some bioassays.

The addition of a second double bond in the A ring leads to yet a further increase in potency. One published synthesis of this compound begins with the hydrogenation of fluorohydrin (**15-2**) to the saturated intermediate (**16-1**). Treatment of that ketone with bromine leads to the dibromide (**16-2**); this reaction, as noted earlier, in fact follows a quite complex pathway involving at one point a 2,2-dibromo derivative.

Dehydrobromination with a base such as collidine then establishes the 1,4-diene function to yield **fluoroprednisolone acetate (19-3)** [13].
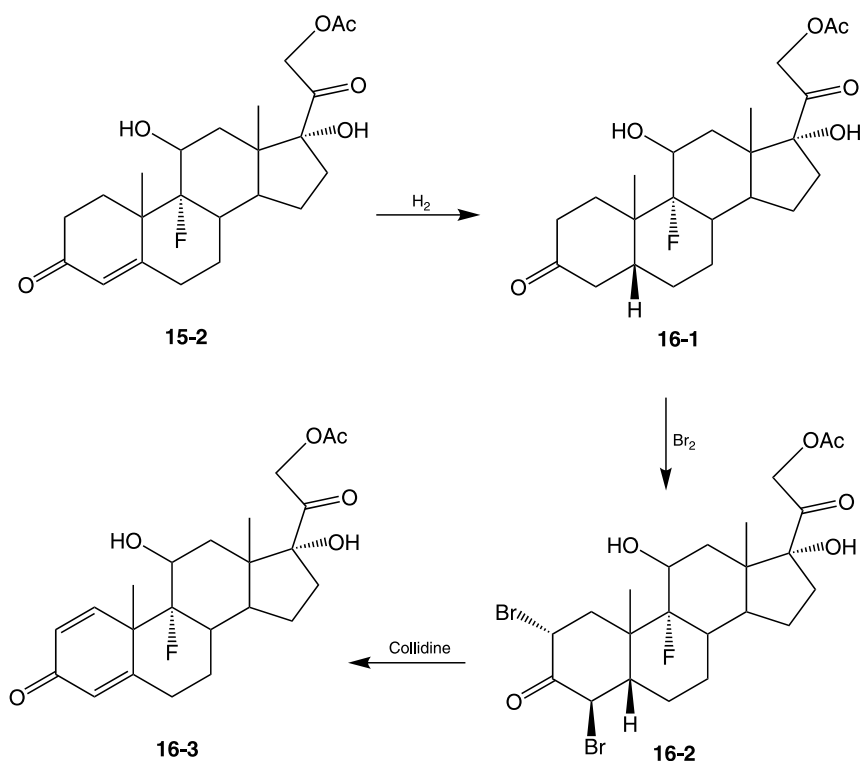
Corticoids that incorporate chlorine at position 9 also show an increase in potency over the corresponding parent drugs bearing hydrogen at that position. The good activity of **dichlorisone** might at first sight seem to indicate that the 11 hydroxy group is dispensable were it not for some evidence to indicate that this halogen is converted to hydroxyl *in vivo*. The compound is prepared in a straightforward manner by
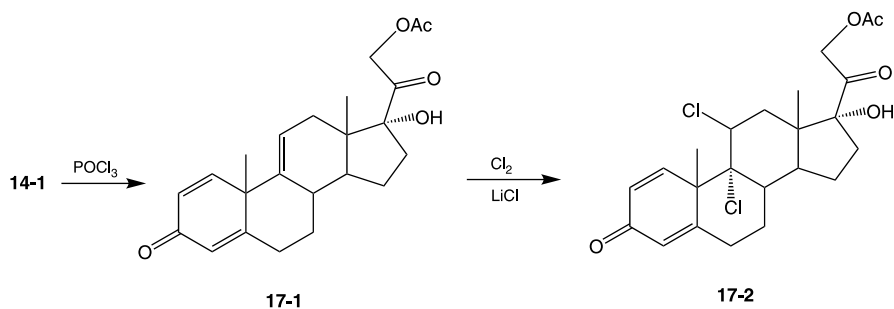
treatment of the triene (**17-1**) from the dehydration of prednisolone acetate with chlorine. The 9α,11β stereochemistry of the product is that which would be predicted from a diaxial opening of a 9α,11α chloronium ion from the initial addition of chlorine from the less hindered side; lithium chloride may provide the anion for starting the ring opening sequence. There is thus obtained the corticoid **dichlorisone acetate** (**17-2**) [14].

Fluorine at the equatorial 6α position also results in an increase in potency. One scheme for the production of such a compound relies on the shift of the double bond from the 4,5 to the 5,6 position, which follows the formation of an acetal at position 3. The scheme starts with the selective reduction of the 11 ketone in the cortisone intermediate (**13-2**). Epoxidation of the product (**18-1**) with a peracid takes place selectively at the unconjugated double bond to give the 5α,6α oxirane (**18-2**). Treatment of that with hydrogen fluoride in tetrahydrofuran leads to fluorohydrin (**18-3**). (There is evidence to indicate that the reagent involves an HF : THF acid : base complex since the omission of THF in at least some cases leads to a complex mixture of rearrangement products [15].) The side chain in fluorohydrin (**18-3**) is then converted
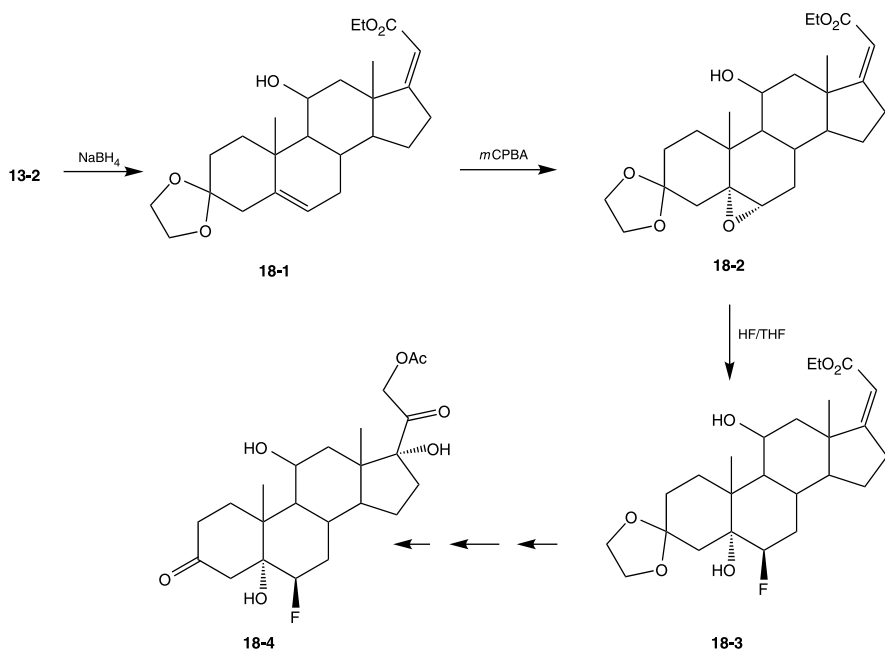
to the dihydroxyacetone derivative (**18-4**) by applying a set of transforms as was done in going from (**13-1**) to (**13-5**). The ester is thus first reduced to an alcohol by means of lithium aluminum hydride and the resulting primary alcohol converted to its acetate. Hydrolysis of the acetonide followed by oxidation of the allylic olefin with a catalytic amount of osmium tetroxide in the presence of NMOP then establishes the required corticoid side chain (**18-4**).

Treatment with a base results in the elimination of the alcohol at the 5 position by what is in effect a reverse Michael reaction to give the enone (**19-1**). The additional

double bond in ring A is then introduced by treating the last intermediate with selenium dioxide to give the 1,4 diene-3-one (**19-2**). The 6-fluoro function, at this point, still occupies the axial β configuration that resulted from the opening of the epoxide. Treatment of (**19-2**) with a strong acid leads the halogen to epimerize to the more stable equatorial 6α position to give **fluprednisolone** (**19-3**) [16].
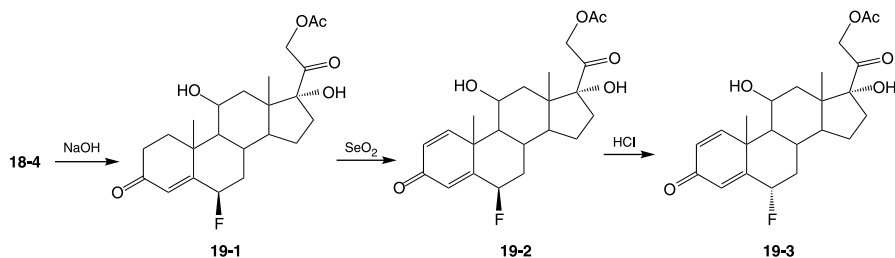
A rather different scheme is used for the preparation of the analogue bearing a methyl group at the 6 position. Since that group is most conveniently incorporated by means of a Grignard reaction, the carbonyl at position 20 needs to be protected first. The protection group used to accomplish this takes advantage of the juxtaposition of two hydroxyl groups next to the side chain ketone at 17. Reaction of the side chain of a typical coritcosteroid (A) with formaldehyde to form a *bis*-methylene-dioxy group (BMD) probably involves the formation of a hemiacetal as the first step. Thus the addition of formaldehyde to the side chain terminal hydroxyl proceeds to form an acetal such as (B). The newly formed hydroxyl group can then add to the adjacent ketone to give a cyclic hemiacetal (C). Reaction of what is now functionally a 1,2 glycol
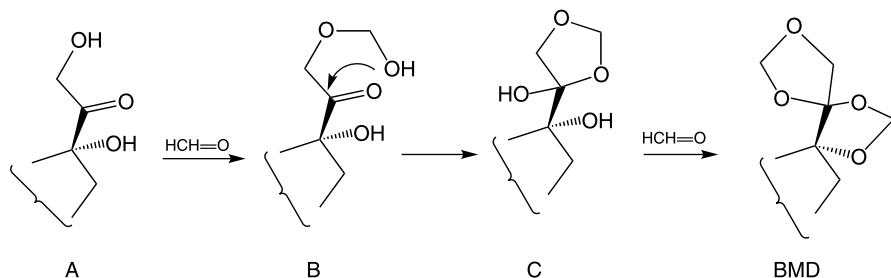
with a second mole of formaldehyde repeats the process and completes the formation of the spirocyclic *bis*-acetal. This protective group, dubbed a BMD, is particularly useful in steroid chemistry as it covers both the ketone and the two adjacent hydroxyl groups.

Reaction of cortisone (**13-5**) with excess formaldehyde thus affords the BMD derivative (**21-1**). The ketone group at the 3 position of the product (**21-1**) is then converted with ethylene glycol to cyclic acetal (**21-2**); **t**he double bond undergoes the customary shift to the 5,6 position. Treatment of the olefin with a peracid such as *meta*-perbenzoic acid gives the 5α,α6 epoxide admixed with a significant amount of its epimer (**21-3**); such a mixture could lead to regioisomers on direct reaction with an organometalic reagent. The alternate route chosen for the introduction of the methyl group at 6 involves first the rearrangement of the mixture of epoxides with formic acid to the 6 ketone (**21-4**).

13-5   21-1   21-2

BMD = *see text*

21-4   21-3
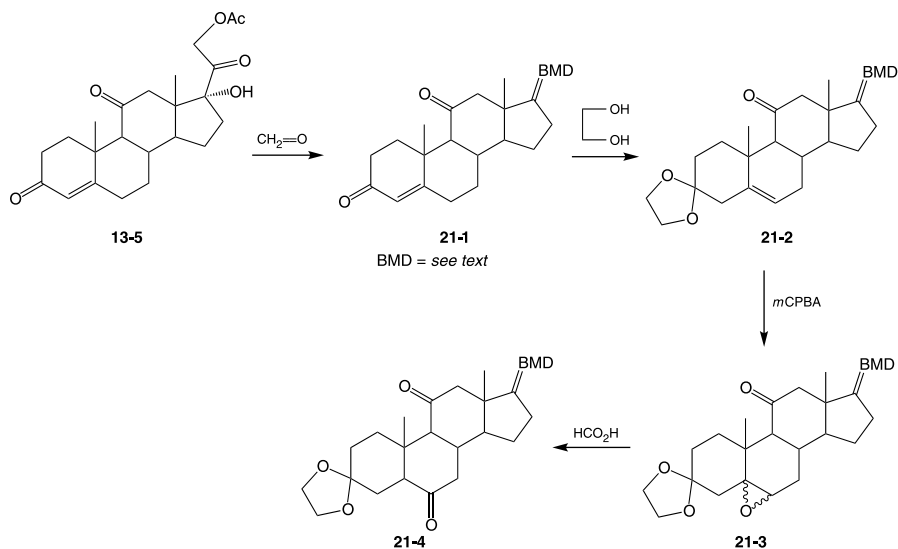
The resulting ketone (**21-4**) is then condensed with methylmagnesium bromide to give the corresponding methyl-carbinol; the highly unreactive nature of the carbonyl group at position 11 is further illustrated by the selective reaction at the 6 position.

21-4   1. CH$_3$MgBr   2. TSA   3. LiAlH$_4$ 22-1   1. H$_3$O$^+$ 2. SeO$_2$ 22-2   AcOH   22-3
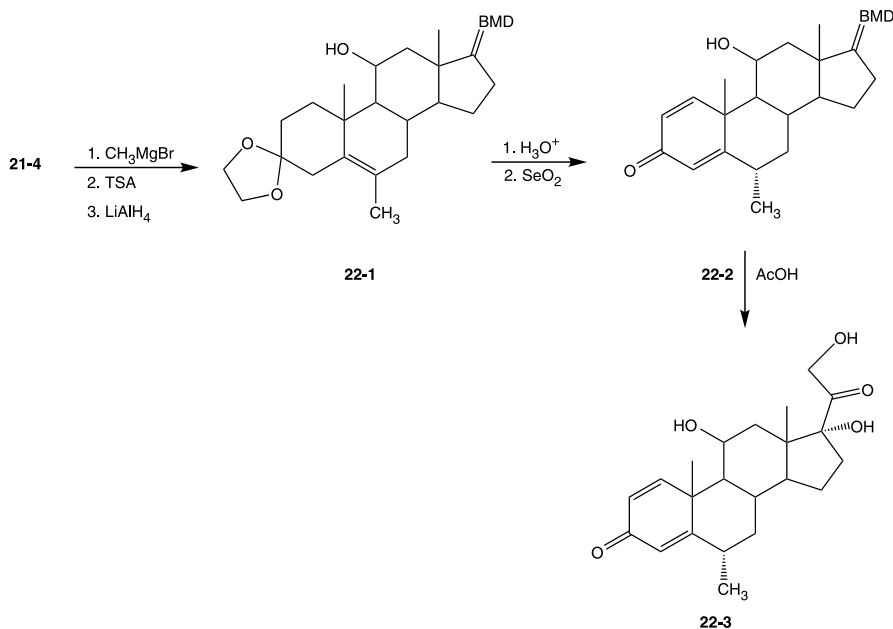
The resulting tertiary alcohol is then dehydrated and the ketone at 11 reduced to an alcohol by means of lithium aluminium hydride to give the intermediate (**22-1**). The acetal is next removed by exchange with acetone in the presence of a dilute acid. The requisite 1,4-diene functionality is then put in place by dehydrogenation

by means of selenium dioxide to give dienone (**22-2**). Removal of the BMD protecting group by treatment with acetic acid completes the synthesis of the widely used corticoid **methylprednisolone** (**22-3**) [17].

Substitution at position 16 also leads to more potent corticosteroids. The additional steric bulk introduced by such substituents adjacent to the dihydroxyacetone side chain also protects that moiety against metabolic degradation. The synthesis used to prepare one compound bearing such a substitution departs from those discussed to this point by deferring the microbiological introduction of oxygen to a relatively late stage. The steps used to incorporate a 16 methylene group very closely parallel those used in the synthesis of melengestrol (**8-4**). The key intermediate (**23-1**) is obtained by the same sequence of reactions for the cycloaddition of diazomethane and pyrolysis starting with pregn-15-enolone acetate. Epoxidation followed by acid catalyzed rearrangement then yields the 17-hydroxy-16-exomethylene array (**23-2**). Saponification of the acetate followed by Oppenauer oxidation of the resulting alcohol leads to the conjugated ketone (**23-3**). The requisite oxygen function is then established by a two-step sequence; reaction of (**23-3**) with bromine takes place selectively at the very reactive methyl group at the 21 position. The displacement of halogen from the thus-formed bromoketone with acetate anion leads to the 21 acetoxy ketone and the intermediate (**23-4**). This in effect constitutes an alternative strategy for building the side chain from that involving the Favorskii rearrangement. The 11 hydroxyl group is then introduced by fermentation of intermediate (**23-4**) with a *Curvularia*. The newly introduced hydroxyl in the product interestingly already has the 11β configuration required for corticoid activity. Dehydrogenation of the product by a further fermentation step [18] yields **prednylene** (**23-5**).
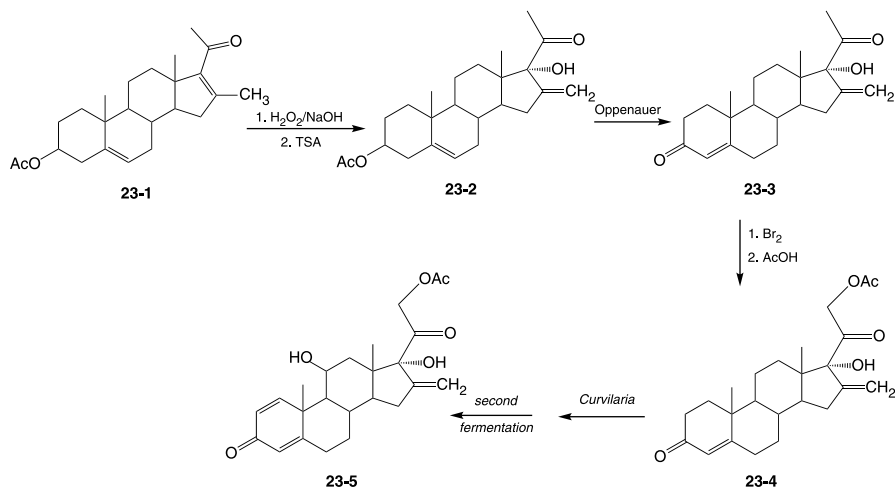
The additive effect of potentiating groups in the corticoid series is aptly illustrated by the fact that **dexamethasone** (**24-3**), which includes a methyl group at 16, fluorine

at 9, and the additional double bond at the 1 position, is close to 100 times as potent as **cortisone** as an anti-inflammatory agent in animal models. The 16β epimer **betamethasone** retains much of this activity, showing about 30 times the potency of **cortisone**. Dehydration of 16β-methylprednisolone acetate [19] (**24-1**) leads to the 9,11 dehydro derivative (**24-2**). The olefin is then converted to the corresponding 9α-bromo-11β-hydrin by means of a source of hypobromite such as basic N-bromosuccinimide and this closed to an epoxide. The standard ring opening reaction with hydrogen fluoride in THF gives **dexamethasone** (**24-3**) [20].
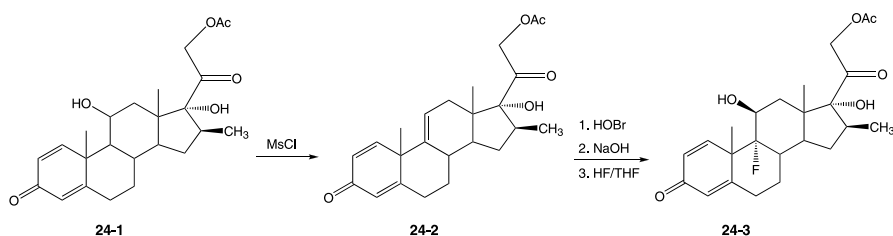
An indication that steric bulk at the 16 position is the more important factor in increases in potency comes from the observation that 16α-hydroxy compounds and their derivatives also show increased potency. The key intermediate in this case is a triene that includes olefins at the 4,5,9,11. and 16,17 positions. The dehydration reactions described thus far involve selective loss of the hydroxyl group at
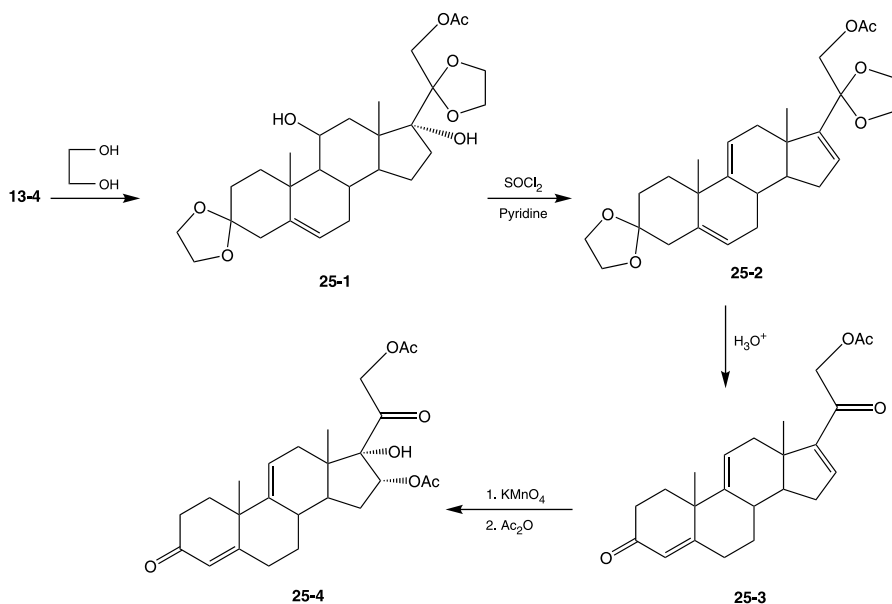
the 11 position. The hydroxyl at 17 is apparently stable under the conditions used. Conversion of the ketone at 20 to its acetal apparently facilitates the loss of the hydroxyl at position 17 as well. The requisite intermediate (**25-1**) is obtained by reaction of hydrocortisone acetate (**13-4**) with ethylene glycol under forcing conditions. That compound goes on to the triene (**25-2**) on exposure to thionyl chloride in pyridine in the cold. The reaction probably proceeds by elimination of the intermediate chlorosulfonate esters since the nature of the hydroxyl groups would seem to preclude those products from going on to the more usual collapse to chloro compounds. The acetal groups are then removed by hydrolysis to give (**25-3**). Oxidation of that compound with osmium tetroxide or, more practically, with potassium permanganate proceeds selectively at the olefin at position 16,17 to give the corresponding 16α,17α diol; reaction with acetic anhydride leads to the diacetate (**25-4**); the stereochemistry is of course dictated by the approach of the reagent from the open side of the molecule.

The 9,11 olefin in the intermediate (**25-4**) is next converted to the 9α-fluoro-11β-hydroxy derivative (**26-1**) by the customary scheme. The additional unsaturation in ring A is then introduced by means of selenium dioxide to afford **triamcinolone** (**26-2**). Reaction of that compound with acetone converts the 16,17 diol to an acetal to afford **triamcinolone acetonide** (**26-3**) [21]. The latter is approximately 50 times more potent than cortisone in animal models; the free glycol interestingly shows only a 2.5-fold increase in potency over the cortisone in the same model.
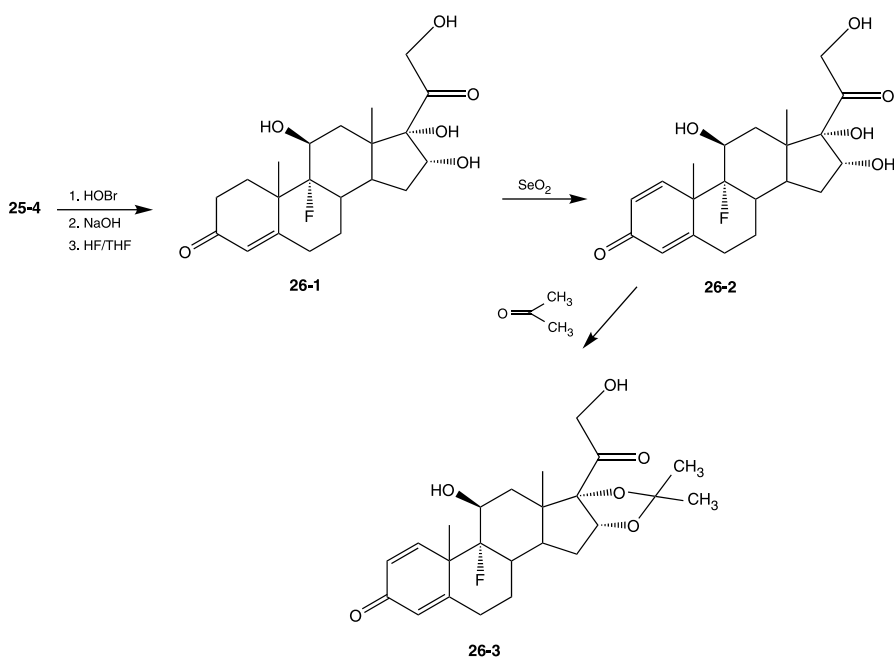
The availability of fairly standardized procedures for the introduction of the various potentiating groups combined with the realization that their biological effects were often additive led to the synthesis of a plethora of highly substituted corticoids. The final steps in the synthesis of corticoid that combines four separate potentiating groups within the same molecule leads to a compound, **flumethasone (27-4)**, that is representative of this work. The synthesis starts with the 16α methyl analogue (**27-1**) of the 6-fluoro corticoid (**19-1**) by using an analogous route for introducing the halogen substituent. The 11-hydroxyl function is then dehydrated to the corresponding olefin (**27-2**); application of the by-now familiar bromohydration, oxirane ring closure, and epoxide opening scheme leads to the intermediate (**27-3**), which now contains two fluorine atoms. Further dehydrogenation of ring A followed by saponification of the acetate at the 21 position affords **flumethasone (27-4)** [22], which shows fully 420 times the potency of cortisone in an animal model for anti-inflammatory activity.
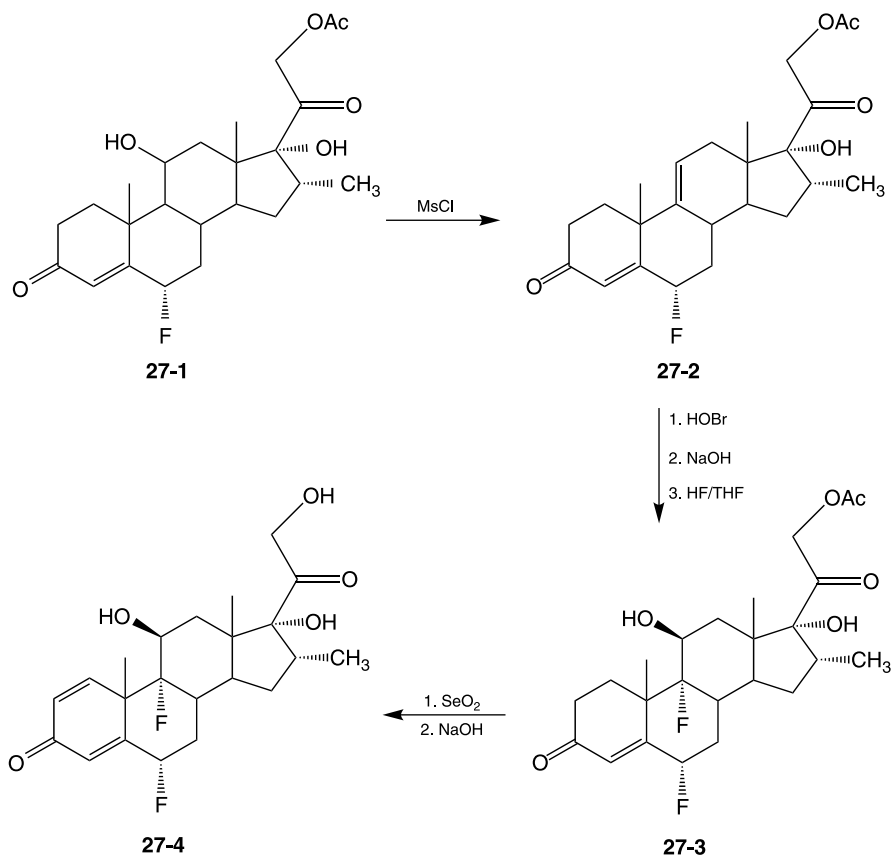
As in the case of the less highly substituted compounds, the acetonide of a 16α hydroxyl corticoid shows about the same potency as its 16α methyl counterpart. Thus, **fluocinonide (28-2)**, obtained by an analogous set of transformations starting with a 6 fluorinated 16 dehydro intermediate (**28-1**) [23], is 440 times as potent as cortisone in the standard assay.
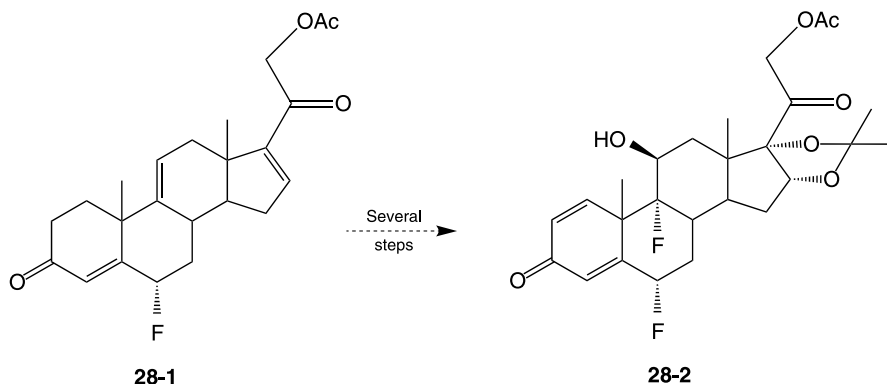
Though corticosteroids are significantly more effective as anti-inflammatory agents than their nonsteroidal counterparts, they are, as a result of the potential for causing serious side effects, usually reserved for treating otherwise intractable inflammation. As noted earlier, corticosteroids inhibit the phospholipases necessary for the elaboration of leukotrienes responsible for the effects of allergy. Corticosteroids are, as a result, quite effective against topical allergic reactions in addition to their effect on inflammation. This is in contrast to the NSAIDS, which are inactive against allergic manifestations by any route of administration. The availability of the extremely potent corticoids, such as those discussed above, has led to their widespread use for treating topical inflammations as well as rashes caused by allergies or insect bites. Leukotrienes are also involved in the asthma-related inflammation of the bronchioles. One important application of corticoids lies in the treatment of asthma by topical application to the lungs by inhalation. While the use of high-potency compounds permits the use of very small doses, there is always the concern that a portion of the drug will enter the circulation via transdermal absorption. These small quantities might at least in theory cause typical corticoid side effects. A means of avoiding effects from even small amounts of drug came from the finding that biological activity was retained in the face of omission of the terminal carbon of the dihydroxyacetone side chain, in effect retaining the carbonyl group as an ester. This led to the design of corticoids with ester moieties at position 17 that would be metabolized by plasma enzymes to acids that, even if absorbed, would be both inactive and quickly cleared from the circulation.

Reaction of the side chain hydroxyacetone in **flumethasone** (**27-4**) with periodic acid leads to cleavage of that function to give carboxylic acid (**29-1**) with the loss of the carbon atom at C-21. Further reaction of the very hindered acid group requires prior activation. Thus, acylation with diphenyl chlorophosphate leads to the mixed anhydride (**29-2**); this is not isolated, but treated immediately with methyl mercaptan. The product, **tibecasone** (**29-3**), is a quite effective topical anti-inflammatory agent [24]. Cleavage of the ester side chain would lead back to the inactive starting acid (**29-1**).
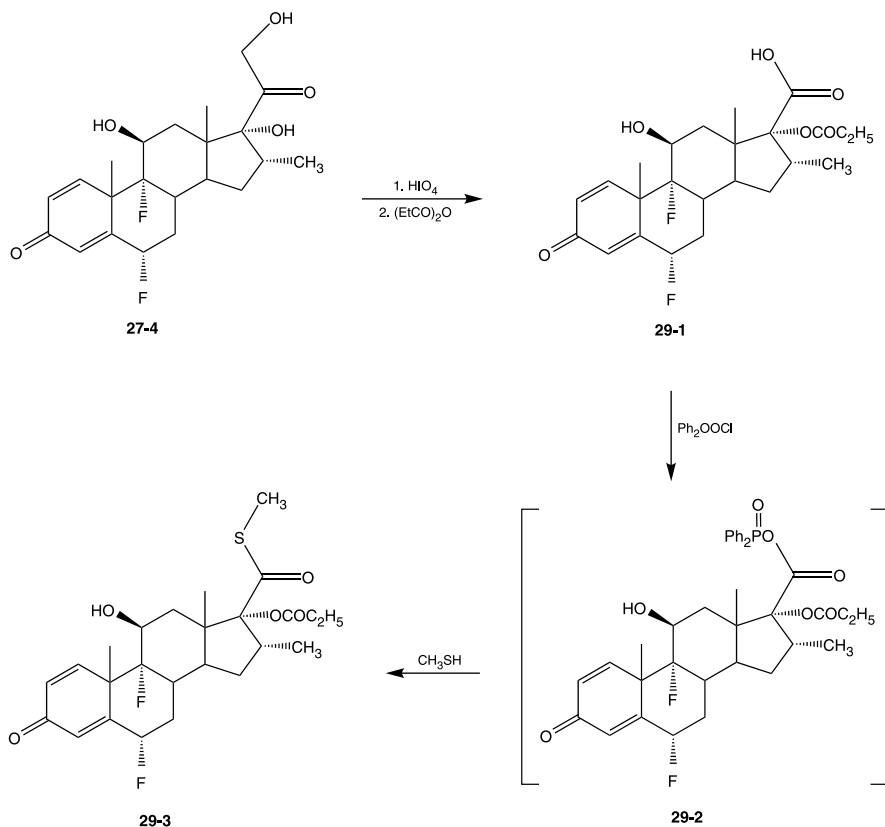
The presence of the fluoromethyl thioester group in **fluticasone** (**30-4**) requires that the carboxyl group in (**29-1**) first be converted to a thioacid. This conversion can be accomplished most conveniently by taking advantage of the rearrangement of a mixed anhydride of (**30-1**) with a carbonylthione. That transient anhydride

(**30-1**) is obtained by reaction of the acid with *N,N*-dimethylformamidoyl chloride; this rearranges to its isomer (**30-2**) under reaction conditions. Saponification of the anhydride under mild conditions selectively cleaves the anhydride to give the thioacid (**30-3**). Alkylation of that intermediate with bromofluoromethane in the presence of a base affords **fluticasone** (**30-4**) [25].
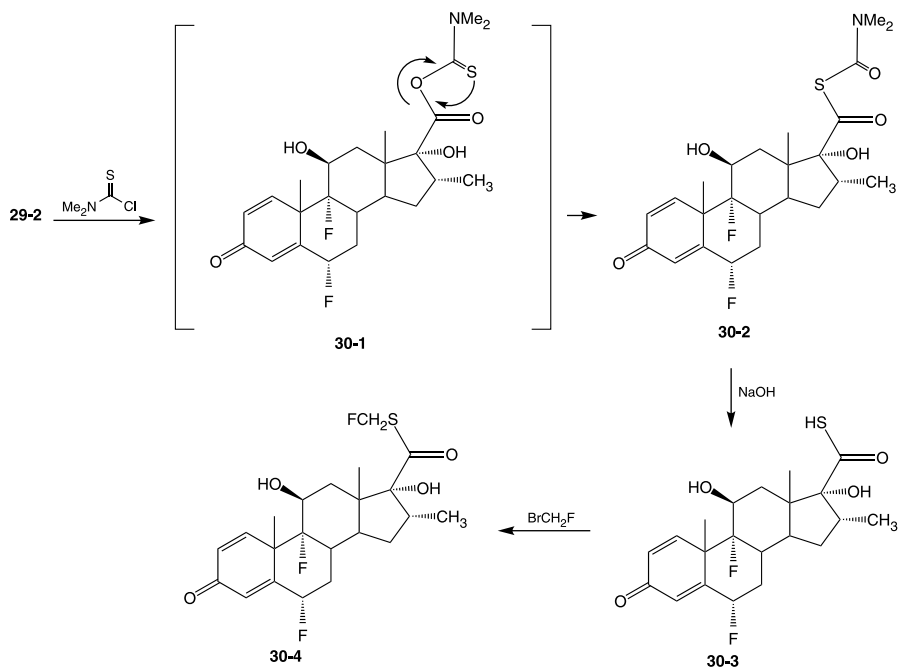
An ester derived from prednisolone has found use as a topical ophthalmic anti-inflammatory drug. Cleavage of the side chain in prednisolone (**31-1**) with sodium periodate affords the corresponding carboxylic acid (**30-2**). Treatment of that product with propionyl chloride affords initially the ester at 17 along with some of the mixed anhydride. The anhydride is then hydrolyzed with a mild base to afford the 17-ester (**31-3**). Alkylation of the carboxylic acid with chloromethylchlorosufonyl chloride (from bromochloromethane and sulfonyl chloride) leads to the chloromethyl ester (**31-4**) and thus **loteprednol** [26].
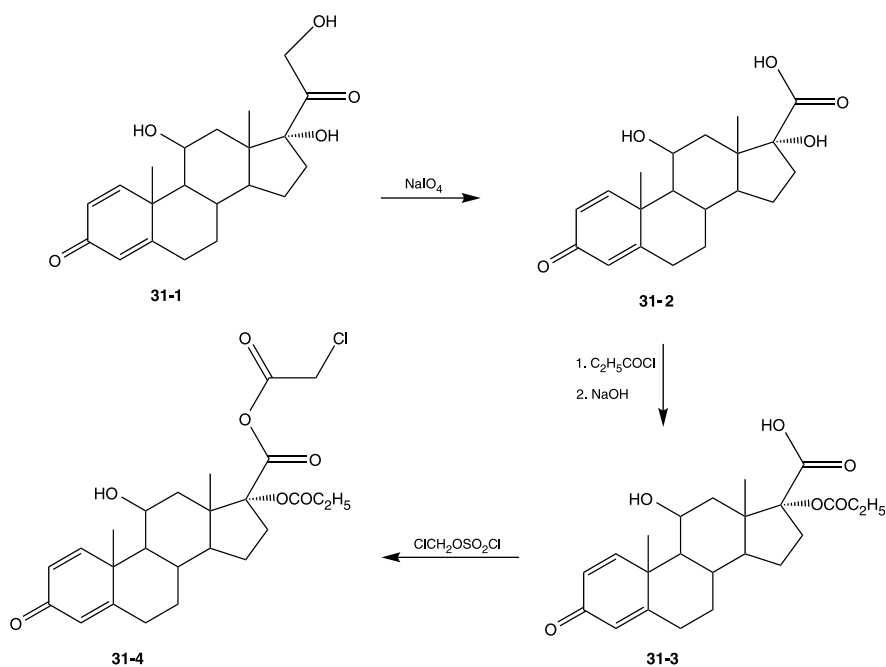
Biological activity is interestingly maintained even in the face of the total omission of a carbonyl group from the side chain. Oxidation of the free alcohol from fluoroprednisolone acetate (**15-2**) under more drastic conditions than those used in the preceding
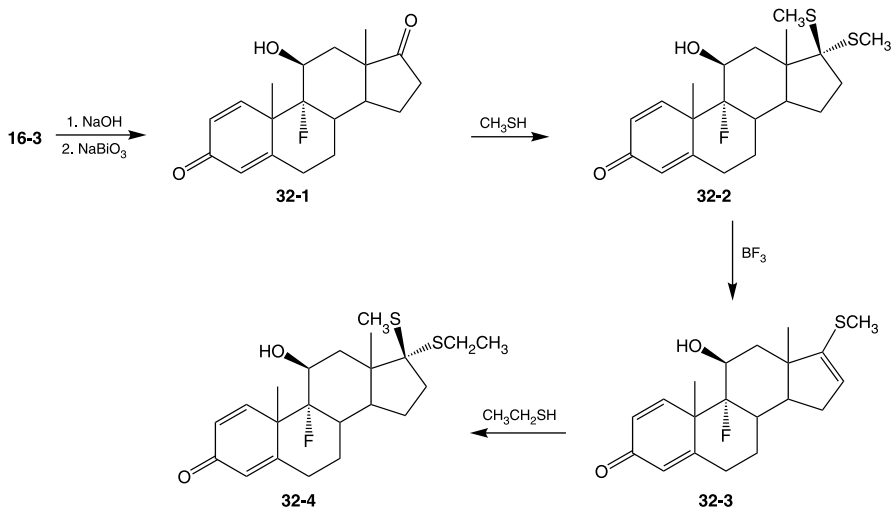
examples with sodium bismuthate leads to a complete loss of the dihydroxyacetone side chain to give the 17-keto derivative (**32-1**). Reaction of that compound with methyl mercaptan leads to the selective formation of the dimethyl thioacetal at the 17 position (**32-2**). Reaction with a strong acid leads to the loss of one of the methyl mercapto groups and the formation of the corresponding 17-thioenol ether (**32-3**). Exposure of that intermediate to ethyl mercaptan results in the formation of the unsymmetrical acetal (**32-4**) **tiprednane** [27]. The stereochemistry follows from the customary addition of ethyl mercaptan from a less hindered face of the steroid.

5.4. COMPOUNDS DERIVED FROM CHOLESTEROL

Many strategies have been followed to control levels of serum cholesterol. The "statins," which inhibit a very early step in the endogenous synthesis of cholesterol, are currently the most widely used family of drugs for that indication. A compound that incorporates the carbon skeleton of cholesterol itself, **colestolone**, is thought to inhibit a late stage in cholesterol synthesis by acting as a product feedback inhibitor. The synthesis starts with the bromination of the allylic 7 position in cholesterol benzoate (**33-1**) by means of *N*-bromo succinimide. Dehydrobromination of the product (**33-2**), for example with collidine, leads to the endocyclic diene (**33-3**). In the presence of a strong acid the bonds migrate to form the transoid 8,9–14,15 diene (**33-4**) in very modest yield. The driving force may be the stability of the all *trans* diene. Oxidation with chromium trioxide interestingly proceeds on the carbon atoms at the extremities of the diene system; the product thus features a hydroxyl group at 9 and a ketone at 15 (**33-5**). Treatment with zinc in acetic acid reductively removes the allylic hydroxyl at 9. Saponification then cleaves the benzoate to afford **colestolone** (**33-6**) [28].
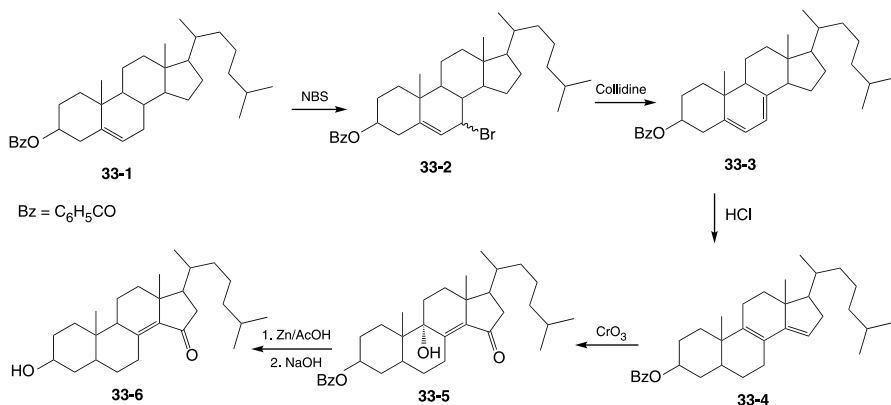
Vitamin D plays a very central role in maintaining the integrity of bone structure. The vitamin actually comprises a set of closely related derivatives of cholesterol that incorporate a 5,7 diene in ring B. The compounds are not actually active per se, requiring activation by ultraviolet light. In a typical example the action of light on

so-called 7-dehydrocholesterol cleaves the bond between rings A and C in a reverse cycloaddition reaction. The initial product undergoes rotation about the former 6,7 bond to lead to a transoid orientation of the exocyclic double bonds. The product, cholecalciferol, which acts as a direct calcium metabolism regulator, is now included as an ingredient in a drug for treating osteoporosis.

7 Dehydrocholesterol   Cholecalciflero
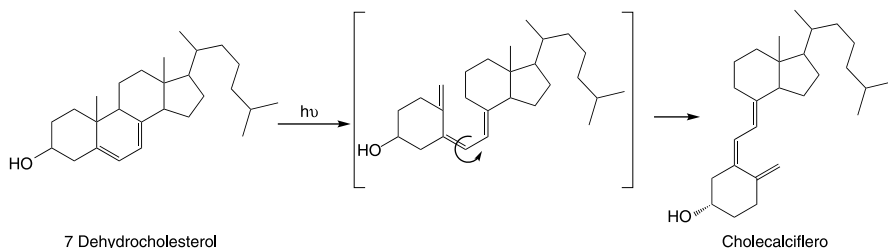
The addition of hydroxyl groups to the side chain is known to increase potency in this series. The starting material (**35-1**) can in principle be obtained from pregnenolone by extension of the side chain by a scheme that starts by addition to the carbonyl group at 20. The diene in ring C can be elaborated by a scheme similar to that used to go from (**33-1**) to (**33-3**). Reaction of the aldehyde in (**35-1**) with isopropenylmagnesium bromide will the lead to carbinol (**33-2**). The double bond is then oxidized to its epoxide (**33-3**). Reduction with lithium aluminum hydride then opens the epoxide to afford the carbinol; removal of the silyl protecting group with a fluoride ion then affords (**33-4**). Irradiation of this last intermediate opens ring B; thermal isomerization then gives the transoid form (**33-5**), **secalciferol** [29].

TMBDS = *tert*-butylsimethylsilyl
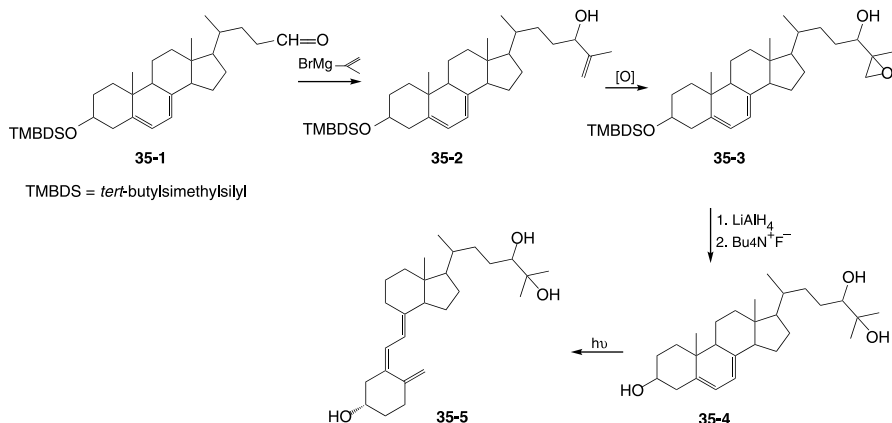
The presence of a hydroxyl group at the 1 position (steroid numbering), which also occurs in a vitamin D metabolite, also enhances potency. The synthesis in this case starts with an advanced ring opened intermediate (**36-5**) already provided with that extra hydroxyl group [30]. Construction of the side chain begins with condensation of the ylide from phosphonium salt (**36-1**) with pivalaldehyde. The ketone in the product (**36-2**) is then reduced to the alcohol (**36-3**). The olefin is then epoxidized

under the Sharpless protocol in the presence of (-) diisopropyl tartrate. The rate of oxidation of the undesired alcohol is sufficiently fast to allow isolation of now-chiral, unreacted **33-3**. The hydroxyl is then protected as its *tert*butyldimethylsilyl (TMBDS) derivative and the olefin cleaved by ozonization to give the protected hydroxyaldehyde (**36-4**). In a convergent sequence, the aldehyde in the vitamin D-like intermediate (**36-5**) is prepared for an *umpolung* reaction by conversion to its *bis* methylselenide (**36-6**). Condensation of the anion from reaction of the selenide with butyl lithium with the side chain synthon (**36-4**) affords the alcohol (**36-7**). The free hydroxyl is then converted to its mesylate. Treatment of the crude product with triethylamine leads to the elimination of the elements of methyselenous acid to leave behind a double bond. A fluoride ion then serves to remove the silyl protecting groups. There is thus obtained the vitamin D analogue **calcipotriene** (**36-8**) [31].
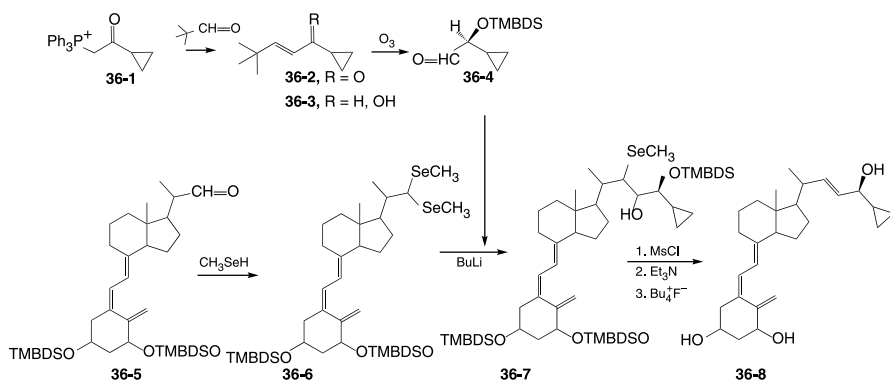
Compounds related to vitamin D are also involved in the regulation of skin growth. One of the vitamins, D3, calcitrol, has been used to treat psoriasis and acne. A recent semi-synthetic vitamin D congener has shown an improved therapeutic index over the natural product. The synthetic sequence to this analogue hinges on the selective scission of the isolated double bond in the side chain. The key step thus involves the inactivation of the conjugated diene centered on ring A. This is accomplished by the formation of a Diels–Alder-like adduct between sulfur dioxide and the starting material (**37-1**), in which the hydroxyl groups are protected as their di-*iso*-propylsilyl ethers [32]. Ozonolysis of the adduct (**37-2**) followed by workup of the ozonide gives the chain shortened aldehyde. Heating the product restores the diene by reversing the original cylcoaddition reaction (**37-3**). The carbonyl group is then reduced to the alcohol by means of borohydride and the resulting alcohol converted to its mesylate (**37-4**). The chain is next homologated by first displacing the mesylate with the anion form diethyl malonate. Saponification of the ester groups followed by heating the product in acid cause the malonic acid to lose carbon dioxide. There is thus obtained the chain extended acid (**37-5**). The carboxyl group is next converted to the activated imidazolide by reaction with carbonyl diimidazole. Condensation of this intermediate

with pyrrolidine gives the corresponding amide. Removal of the silyl protection groups with fluoride leads to **ecalcidine** (**37-6**) [33].
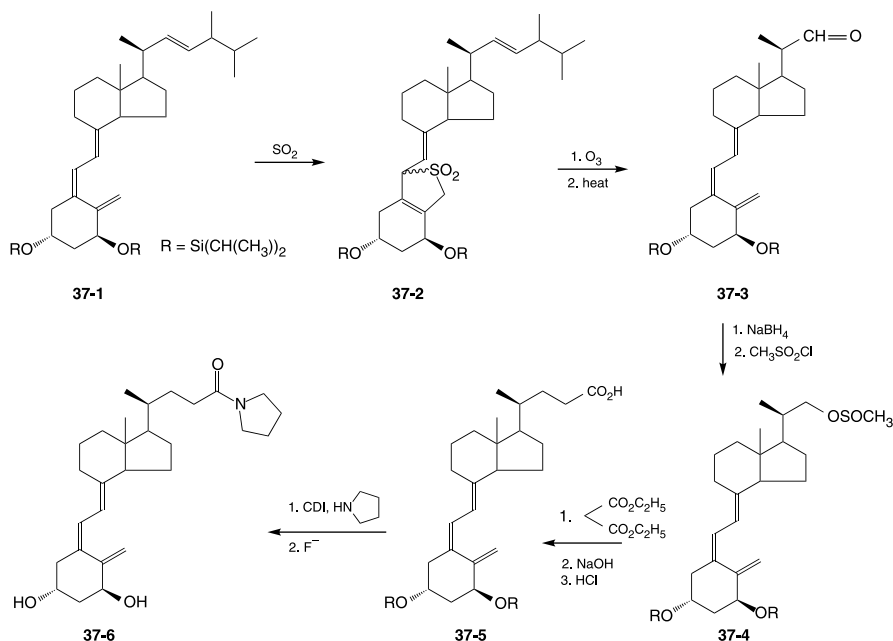
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CHAPTER 6

NONSTEROIDAL SEX HORMONES AND THEIR ANTAGONISTS

6.1. INTRODUCTION

The gonadal hormones, that is, estrogens, progestins, and androgens, play a pivotal role in the reproductive life of all mammals. These steroids also control related functions such as, for example, support of secondary sex characteristics. Nonsteroidal counterparts for these hormones were initially sought as more readily accessible than the steroid-based agents. Estrogens were the first to yield results in that search. The almost adventitious discovery of structurally related nonsteroidal antagonists combined with utility in treating estrogen responsive tumors greatly expanded work in this area. Nonsteroidal progestins and androgens turned out to be more elusive targets: the discovery of a pair of nonsteroidal compounds that bind to androgen receptors as well as an agent that is recognized by progestin receptors dates within the past decade.

6.2. ESTROGENS

6.2.1. Nonsteroidal Estrogens

Synthetic estrogens and their antagonists represent a small but important class of drugs, a group of compounds that is finding extensive use in the treatment of breast cancer and is increasingly prescribed for treating osteoporosis in women. The structures of these compounds at first sight comprise a much more heterogeneous

collection of structures than their steroid counterparts. Even a cursory examination will quickly disclose the fact that they all incorporate a common pharmacophore: a stilbene or a 1,2-diphenylethane moiety. In the case of the antagonists, one of the benzene rings bears a short side that terminates in a polar function. Both the nonsteroidal agonists and antagonists have been further shown to bind to estrogen receptors.

It became apparent as soon as the estrogens were isolated, in the early 1930s, that these were extremely potent compounds that could have important, and then as yet unidentified, therapeutic applications. It was also realized that the isolation of adequate supplies from natural sources would be difficult because of the low levels at which they occur. Preparation of estrone or estradiol proper by total synthesis was ruled out by the fact that the full structure had yet to be established. The body of synthetic methods known in the early 1930s would probably have been unequal to the task even if the full, detailed structure had been known. It had been observed that steroids yielded polycyclic hydrocarbons such as the phenanthrene derivative (**1-1**) on destructive distillation, a compound also obtained from the degradation of cholesterol. The search for practical nonsteroidal estrogens was given impetus by the finding that the structurally related phenanthrene derivative (**1-2**) showed estrogenic activity in animal models [1].
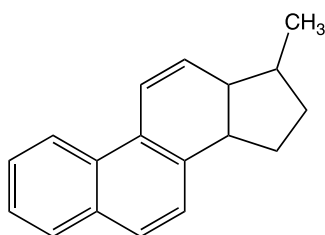
1-1   **1-2**
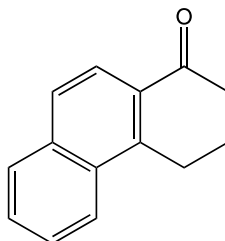
Diethylstibestrol (**2-6**), also known as DES, was one of the first practical nonsteroidal estrogenic drugs. The agent was at one time widely used—and too often misused—for the treatment of a number of hormone-related disease states. The very belated discovery that the drug elicited cancers in daughters of women who had been prescribed it drug during pregnancy virtually ended the use of this drug. The one-time widespread use of DES led to the development of a large number of syntheses for that compound. One of those starts with the chlorination of the benzylic position of *para*-ethylanisole (**2-1**) with *N*-chlorosuccinimide (**2-2**). Treatment of that intermediate with sodium amide in liquid ammonia leads initially to the formation of a carbanion (**2-3**) at the benzylic position by abstraction of a proton. This anion then displaces chlorine on a second molecule of the halide; this results in net alkylation and the formation of the transient chlorinated dimer (**2-4**). Dehydrochlorination of (**2-4**) by excess amide leads to the formation of stilbene (**2-5**) as a mixture that consists predominantly of the desired *trans* isomer. The steric outcome of this reaction suggests that the alkylation product consists largely of the *erythro* isomer, indicating that the alkylation step leads to the least crowded intermediate.

Demethylation of the stilbene (**2-5**) by means of hydrogen bromide in acetic acid leads to DES (**2-8**) [2].
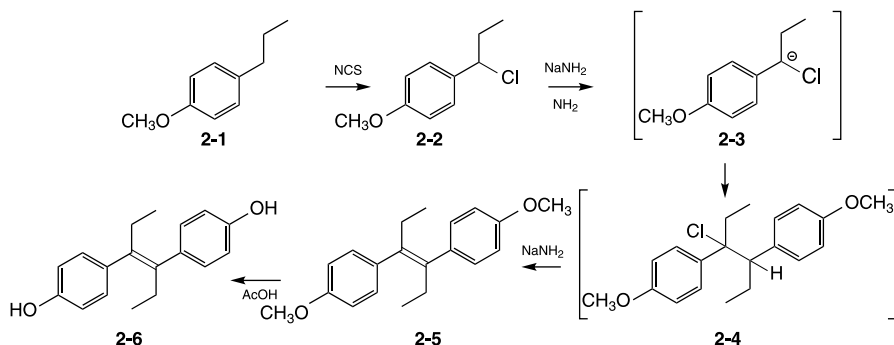
The estrogenic activity of DES has been attributed to its very general structural mimicry of estradiol, where one of the phenolic rings acts as a surrogate A ring and the other fills in for the cyclopentano moiety. The relatively rigid stilbene frame-work then serves to hold those rings in place while supplying the required steric bulk. It was generally accepted that the compound interacted with a receptor for estradiol long before those entities were actually identified. More recent investigations have shown that DES and related synthetic estrogens have binding constants with estrogen receptors that, for selected compounds, exceed those of the endogenous hormones. This class is unique among steroid receptors because of its wide tolerance for struc-tural modifications, as will be noted from the structures of the estrogen antagonists. It also stood out until quite recently due to the fact that receptors for the other classes of steroids failed to show appreciable binding with nonsteroidal compounds.

The conjugated diene system in the synthetic estrogen **dienestrol** (**3-3**) should provide even greater rigidity than the stilbene bond in (**2-8**). The key intermediate (**3-2**) is obtained in a straightforward manner by pinacol coupling of the substituted propiophenone (**3-1**). Dehydration of the thus-obtained glycol (**3-2**) with a mixture of acetyl chloride and acetic anhydride leads to the transoid diene system; saponification removes the acetate groups and thus affords **dienestrol** (**3-3**) [3].
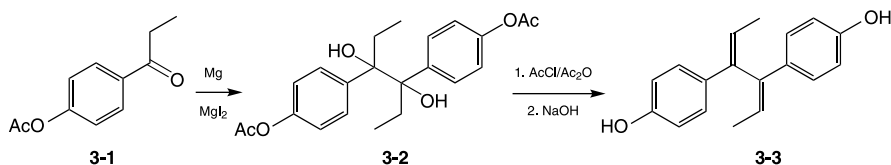
This sequence bears an interesting resemblance to a one-step coupling reaction developed many decades later, a transform that would seem applicable to the syn-thesis of DES if that were still an important drug. Thus, treatment of acetophenone (**4-1**) with titanium trichloride has been demonstrated to yield initially the pinacol product (**4-2**); if a reducing agent such as potassium metal is present, the glycol is eliminated to form a double bond. The product (**4-3**) consists predominantly (~90%) of the *trans* isomer [4].

4-1   4-2   4-3
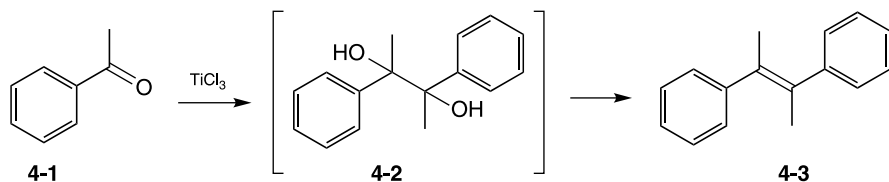
The two examples that follow owe their significance mainly to the fact that they led to the development of the much more important estrogen antagonists. The finding that the unsubstituted hydrocarbon triphenylethylene showed some activity in animal models as an estrogen aptly illustrates the nonspecific nature of the estrogen receptor. Adding methoxyl groups to the *para* positions of the hydrocarbon (**5-3**) increases lipophilicity and thus leads to an increase in potency. Condensation of the Grignard reagent from 4-bromomethylanisole with anisophenone (**5-1**) gives the

5-1   5-2

5-3   5-3
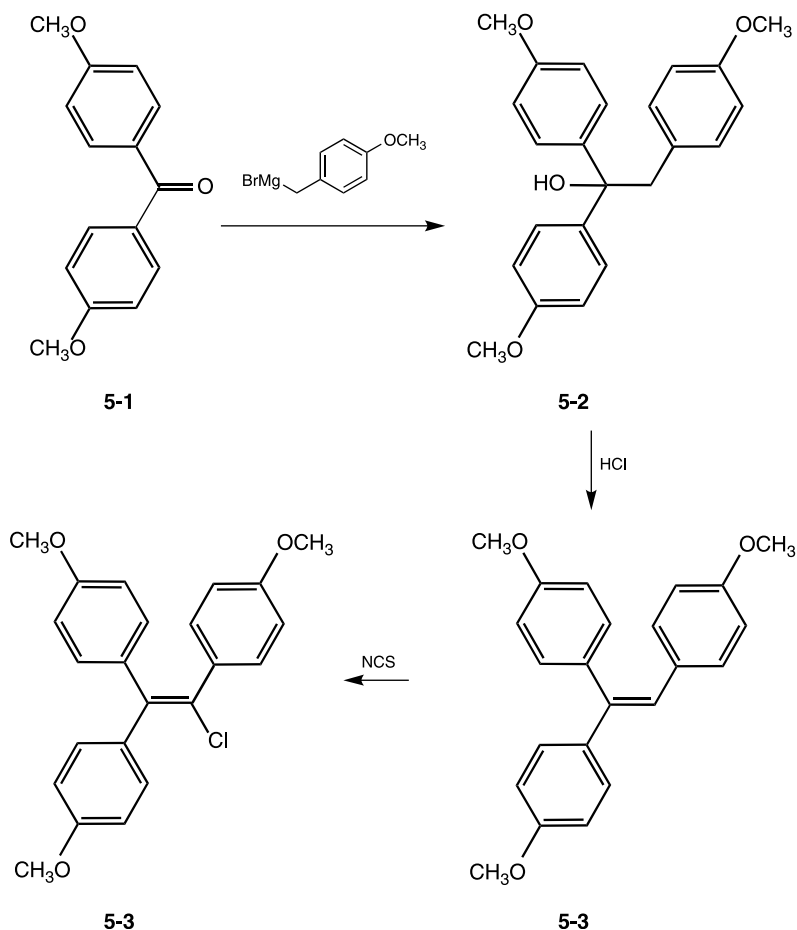
alcohol (**5-2**). Treatment of the tertiary alcohol with acid leads to the formation of the triarylethylene, trianisene (**5-3**) [5]. Replacement of the remaining hydrogen on the

ethylene by chlorine by reaction of (**5-3**) with *N*-chlorosuccinimide leads to **chlorotrianisene** (**5-4**) [6]. This replacement leads to another increase in potency, perhaps by providing the additional bulk.

6.2.2. Nonsteroid Estrogen Antagonists

6.2.2.1. Arylethylenes. Incorporation of a side chain bearing basic nitrogen in a molecule closely related to **chlorotrianisene** markedly changes the biological properties. While the compound still interacts with the estrogen receptor, it largely blocks the effects of endogenous or exogenous estrogens. This activity of the prototype, **clomiphene** (**6-4, 6-5**), is less clear than that of later congeners because it in fact consists of a mixture of geometric isomers only one of which is an antagonist. The observation that this compound showed contraceptive activity in rats by inhibiting the estrogen dependent implantation of fertilized ova led to the first concentrated research effort in this area. The known dependence on estrogen of the majority of breast cancers provided additional motivation for one research group. This research led to **tamoxifen** (**9-3**), an important drug for adjuvant therapy of mammary cancer. The original goal, the development of a nonsteroidal antifertility compound, was fulfilled in India by the approval, over a decade ago, of the use of the anti-estrogen **ormoloxifene** (**20-8**) (formerly known as **centchroman**) as an oral contraceptive.

The synthetic route to **clomiphene** is in fact very close to that used for its nonbasic parent. The basic side chain, usually referred to as a basic ether, is incorporated in the first step by alkylation of the phenol in 4-hydroxybenzophenone (**6-1**) with 2-chlorotriethylamine. The addition of benzylmagnesium bromide to the product (**6-2**) affords the tertiary alcohol (**6-3**).

6-1   6-2   6-3
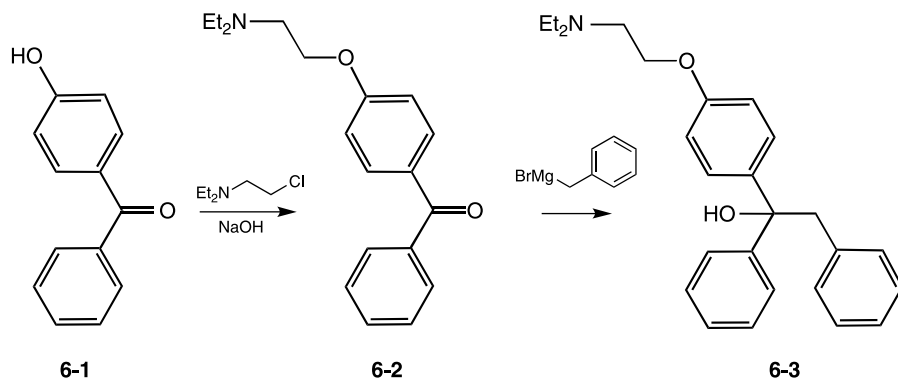
The known preference for *transoid* elimination of the elements of water from alcohols such as (**6-3**) controls the stereochemistry of the product. The arrangement in the starting material of the groups about the incipient olefin actually determines the steric identity of the product. The two rotamers of alcohol (**6-3**) that have the *trans* hydrogen and hydroxyl shown as their Newman projections (**6-3a**) and (**6-3b**) are equally probable since they differ only in the placement of the remote basic ether. The dehydration in fact gives a mixture of the *trans* isomer (**7-2**) and the *cis* isomer (**7-3**) presumably from rotamers (**6-3a**) and (**6-3b**), respectively. Reaction

of the mixture with *N*-chlorosuccinimide gives a mixture of the chlorinated derivatives [7]; commercial **clomiphene** in fact consists of an approximately 6 : 4 mixture of the isomers (**7-4**) and (**7-5**). It was determined later that the Z isomer (**7-4**) acts as an estrogen antagonist while the isomer (**7-5**) retains considerable agonist activity. The mixture is, however, quite effective in inducing ovulation in cases of infertility, the approved indication for this drug.
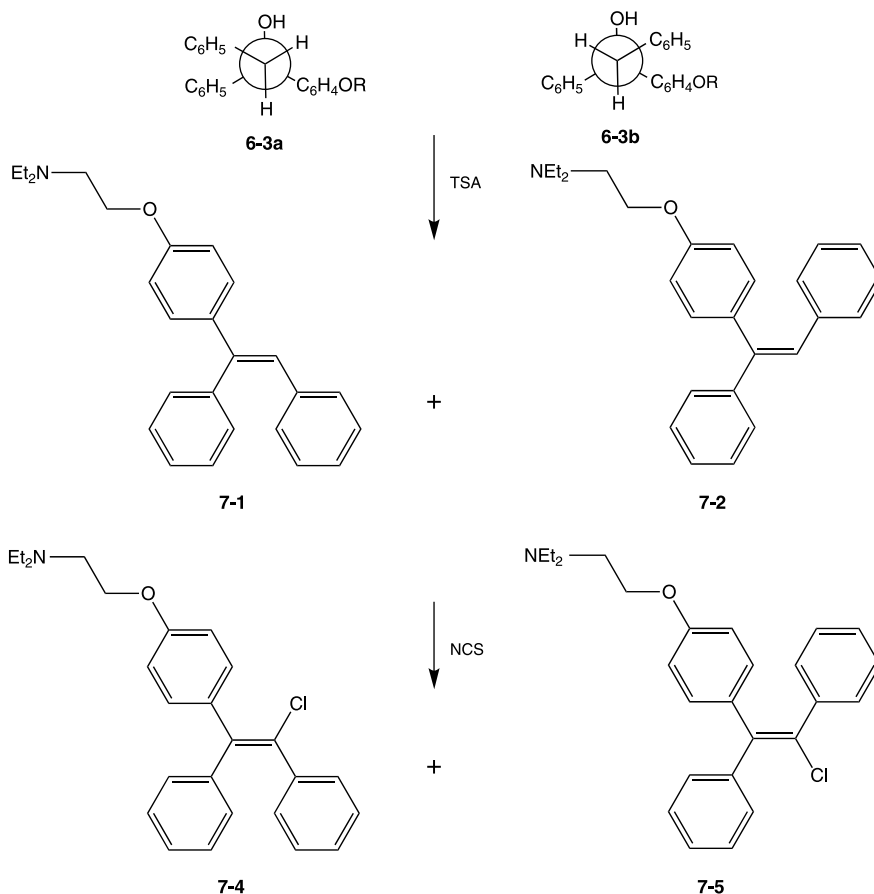
Essentially the same route is followed for the synthesis of the triphenylethylene **nitromifene** (**8-5**). The sequence starts with Friedel–Crafts acylation of the alkylation product (**8-1**) from phenol and 1,2-dibromoethane with the acid chloride from anisic acid (**8-2**). The displacement of bromine in the product (**8-3**) with pyrrolidine leads to the formation of the basic ether and thus (**8-4**). Condensation of that product with benzylmagnesium bromide gives the tertiary alcohol (**8-5**). This product is then treated with a mixture of nitric and acetic acids. The dehydration products from the first step almost certainly consist of a mixture of the E and Z isomers for the same reasons advanced above. The olefin undergoes nitration under reaction conditions to lead to **nitromifene** (**8-6**) as a mixture of isomers [8]; the separated compounds are reported to show surprisingly equivalent agonist/antagonist activities.
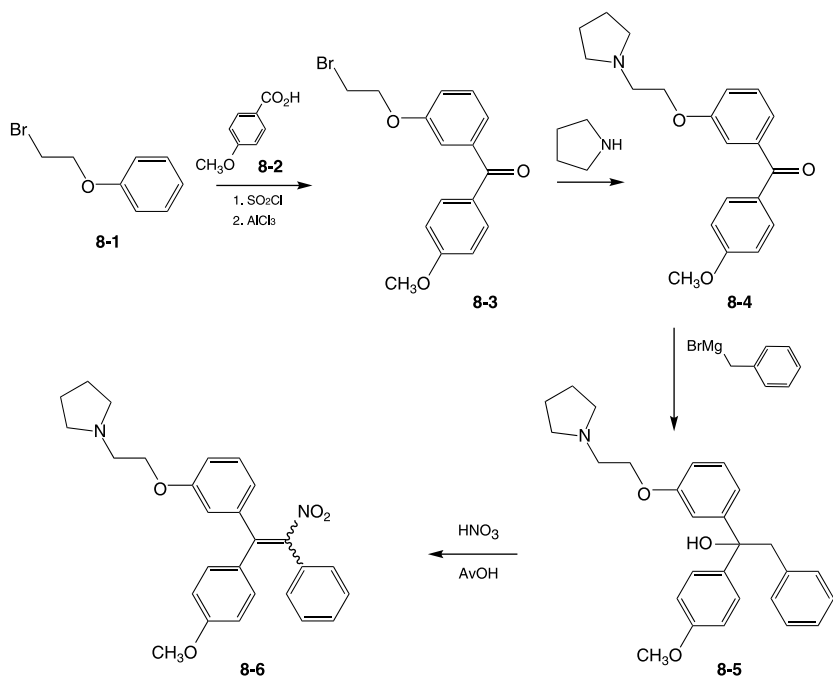
Though the preparation of the estrogen antagonist **tamoxifen** (**9-3**) appears to be comparable to the foregoing, the presence of the ethyl substituent on the ethylene has important stereochemical consequences. The sequence also differs from the foregoing by starting with an intermediate (**9-1**) that already includes both carbons of the
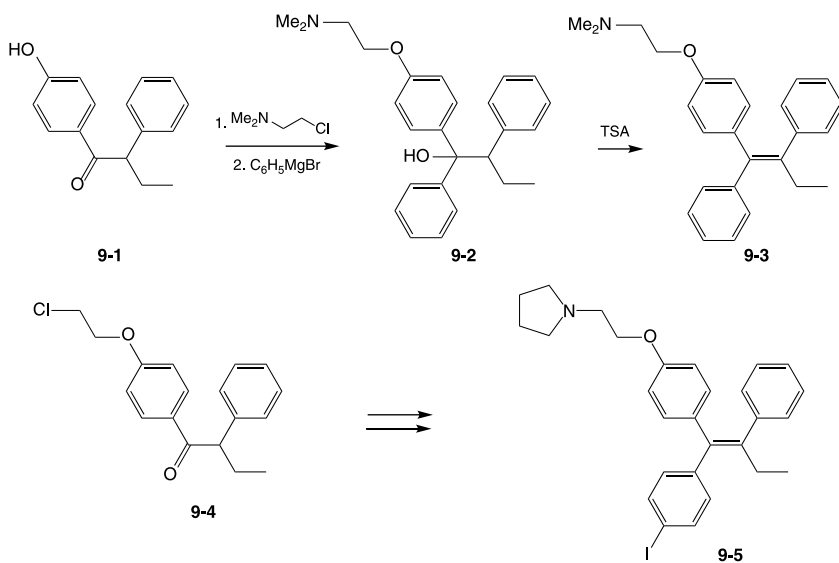
future ethylene moiety. The substituted desoxybenzoin (**9-1**) is first alkylated to its basic ether with 2-chlorotriethylamine. Reaction with phenylmagnesium bromide leads to the corresponding tertiary alcohol (**9-2**). Dehydration by means of *p*-toluene-sulfonic acid gives the triphenylethylene, this time as predominantly the Z isomer **tamoxifen** (**9-3**) [9]. Isomerically pure tamoxifen is a potent estrogen antagonist with little intrinsic agonist activity; the E isomer, by contrast, displays virtually only estrogen agonist activity.

The stereochemical outcome of this sequence traces back to the Grignard addition step. The rotamer of the starting ketone (**10-1**), which involves the fewest nonbonding interactions, is that which opposes the two aromatic rings as shown in the Newman projection below. Isomer (**10-2a**) will be formed if it is assumed that the organo-metallic adds from that direction, which will lead to the fewest steric interactions in the product giving (**10-2a**). The rotamer (**10-2b**) from this product, which has the *trans* hydroxyl-proton relation required for dehydration, leads to the observed product (**9-3**).
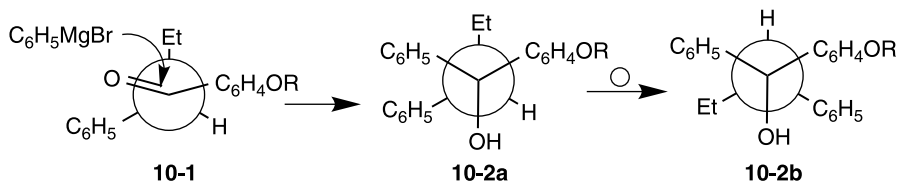
A variant on the sequence in which the third aromatic ring is introduced by reaction of the ketone in chloroethyl ether (**9-4**) with the lithio reagent from 1-4-di-iodobenzene leads in several steps to **iodoxifene** (**9-5**) [10]. 4-Hydroxy-tamoxifen, in which a hydroxyl group has been introduced on one of the benzene rings, comprises one of the principal metabolites of the drug. The "unnatural" *meta* isomer of
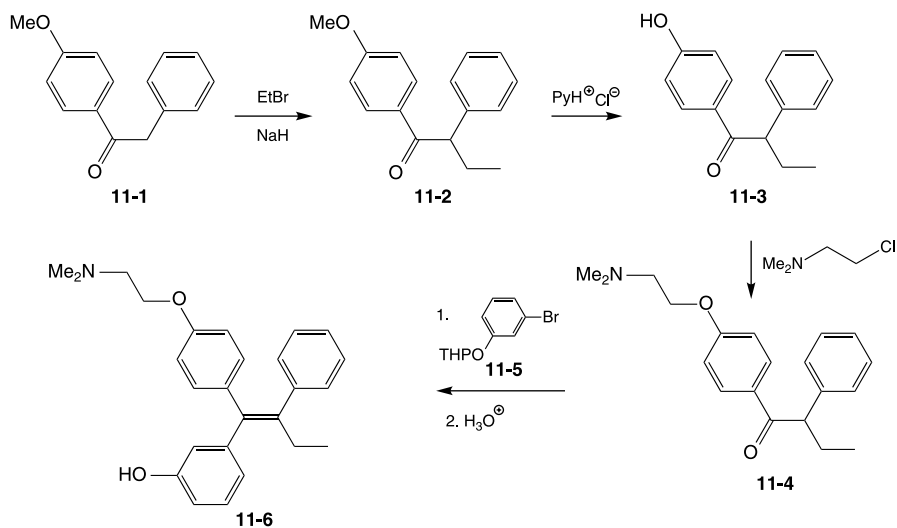
that metabolite has much the same activity as tamoxifen itself. The synthesis of that compound begins with the alkylation of 4-methoxydesoxybenzoin (**11-1**) with ethyl bromide in the presence of sodium hydride to afford (**11-2**). The methyl ether is then cleaved with pyridinium hydrochloride to afford the free phenol (**11-3**). The newly formed hydroxyl group is then alkylated with dimethylchloromethylamine to afford the corresponding basic ether (**11-4**). The ketone in (**11-4**) is next allowed to react with the Grignard reagent from the tetrahydropyranyl ether of *meta*-bromo-phenol (**11-5**). Exposure of the addition product to aqueous acid leads to the hydroly-sis of the ether as well as the dehydration of the teriary benzylic carbinol. Separation of the E isomer from the mixture of stereoisomers then affords the estrogen antagonist **droloxifene** (**11-6**) [11].

Some recent work on estrogen antagonists takes advantage of the stereochemical control afforded by starting with preformed ethylene fragments. Alkylation of desoxybenzoin proper (**12-1**) with the benzyl ether from 2-bromoethanol affords the intermediate (**12-2**). This is then condensed with the Grignard reagent from the tetra-hydropyranyl ether of 4-bromophenol (**12-3**) to give the corresponding tertiary alcohol. Since this is quite analogous with the reaction leading to (**9-3**), this would be expected to consist predominantly of a single diastereomer. The benzyl ether protecting group is then removed by hydrogenation over palladium to yield the diol (**12-4**). A strong acid leads to the formation of a tetrahdrofuran ring from the tertiary alcohol, and that on the ethyl side chain as well as hydrolysis of the terahydro-pyranyl protecting group forms (**12-5**). Ring formation almost certainly starts by loss of the protonated benzhydryl hydroxyl group; the fact that the final olefin consists of predominantly the Z isomer argues that that stereochemical identity must be retained during ring formation. This can be rationalized by assuming that a loss of the
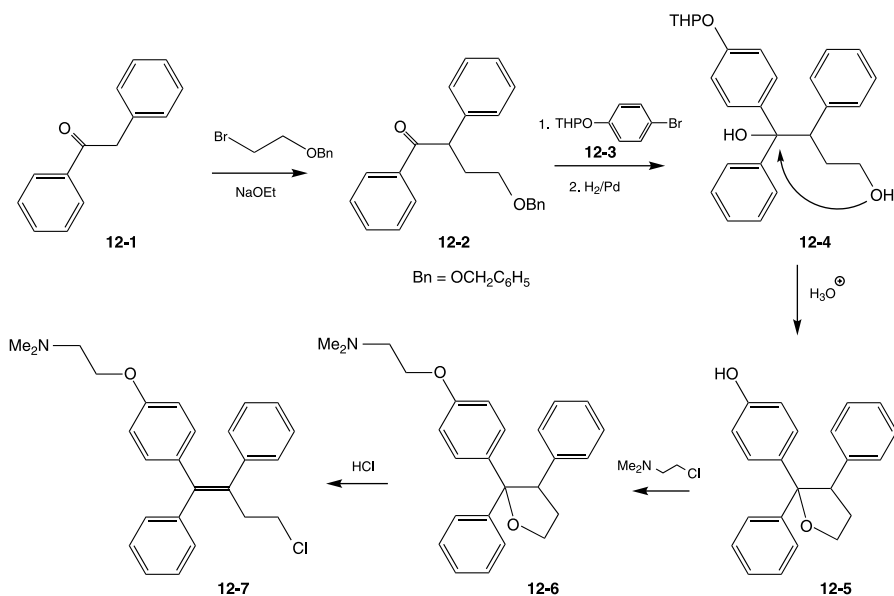
benzhydryl hydroxyl is simultaneous with an attack by the terminal primary alcohol. The requisite basic ether is then added by alkyation of the free phenol with 2-chlorotrimethylamine to afford (**12-6**). Treatment of this last intermediate with hydrogen chloride leads to a ring opening of the tertrahydrofuran ring with simultaneous formation of the Z olefin; the terminal oxygen is converted to a chloro substituent under the reaction conditions. There is thus obtained the estrogen antagonist **toremifene** (**12-7**) [12].

Virtually all estrogen antagonists that have been studied in any detail incorporate a basic side chain in the form of a tertiary-aminoethoxy aromatic ether. An exception, published in the late 1960s, reported that the amine could be replaced by a glycol [13]. The estrogen antagonist **ospemifene** takes this one step further. Antiestrogenic activity is retained when the basic ether in the antagonist **toremifene** (**12-7**) is replaced by a simple hydroxyethyl group. This agent is prepared starting with an intermediate (**12-5**) used to prepare (**12-7**). Reaction of that compound with a strong acid leads to a ring opening of the saturated furan with a concomitant formation of the olefin (**13-1**). Alkylation of the phenol in (**13-1**) with the chloro-ethanol benzyl ether affords (**13-2**). The free hydroxyl at the end of the chain is then converted to the halide (**13-3**) by reaction with carbon tetrachloride and triphenyl phosphine. Removal of the benzyl group by means of hydrogen over palladium then affords **ospemifene** (**13-4**) [14].
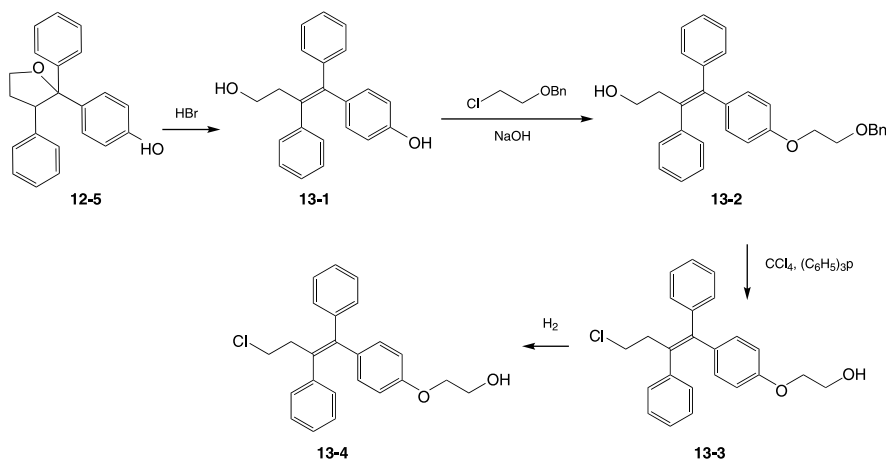
6.2.2.2. Carbocyclic Ethylenes Fused to a Benzene Ring.

Compounds designed as rigid or conformationally constrained analogues have provided several classes of very potent estrogen antagonists. The fused bicyclic moieties chosen to lock these compounds, it should be noted, more closely resemble the steroid AB ring moiety than do the styrene fragments of the open chain analogues discussed above.

One synthesis of the potent estrogen antagonist **nafoxidine** (**14-9**) [15] involves assembly of the full carbon skeleton prior to formation of the bicyclic nucleus.

The first product isolated from the reaction of the deoxybenzoin (**14-1**) with ethyl formate and sodium ethoxide consists of the sodium salt (**14-2**) of the enol from the β-formyl derivative. That salt is then reacted without prior purification with the phosphonium salt (**14-4**) from 3-methoxybenzyl bromide (**14-3**) and triphenyl-phosphine. These reaction conditions result in net Wittig condensation to afford the enone (**14-5**) as an undefined mixture of isomers. The small amount of enolate (**14-2**) present in solution in the essentially heterogeneous mixture probably reacts on the surface of the phosphonium salt to form a small amount of phosphorane; that then condenses with the minor fraction of neutral (**14-2**) present as the keto-aldehyde tautomer. (The reaction gives intractable mixtures when carried out in the traditional manner by preforming the ylide.) Catalytic reduction then affords the enone (**14-5**). Selective demethylation of the methyl ether on the future 1-aryl ring to give phenol (**14-6**) is achieved by reaction of the compound with three equiva-lents—one for each oxygen—of aluminum chloride; the ether directly *para* to the carbonyl is sufficiently more electron deficient so as to cleave preferentially. The ketone is then cyclized by heating in the presence of toluenesulfonic acid to give dihydronaphthalene (**14-7**). Alkylation with *N*-choroethylpyrrolidine (**14-8**) of the salt obtained by treating the phenol with sodium hydride affords **nafoxidine** (**14-9**). Catalytic hydrogenation of that product then gives the tetralin (**14-10**) [15]. Reaction of that product with boron tribromide results in the cleavage of the methyl ether in the fused ring to give **lasoxifene** (**14-11**) [16].
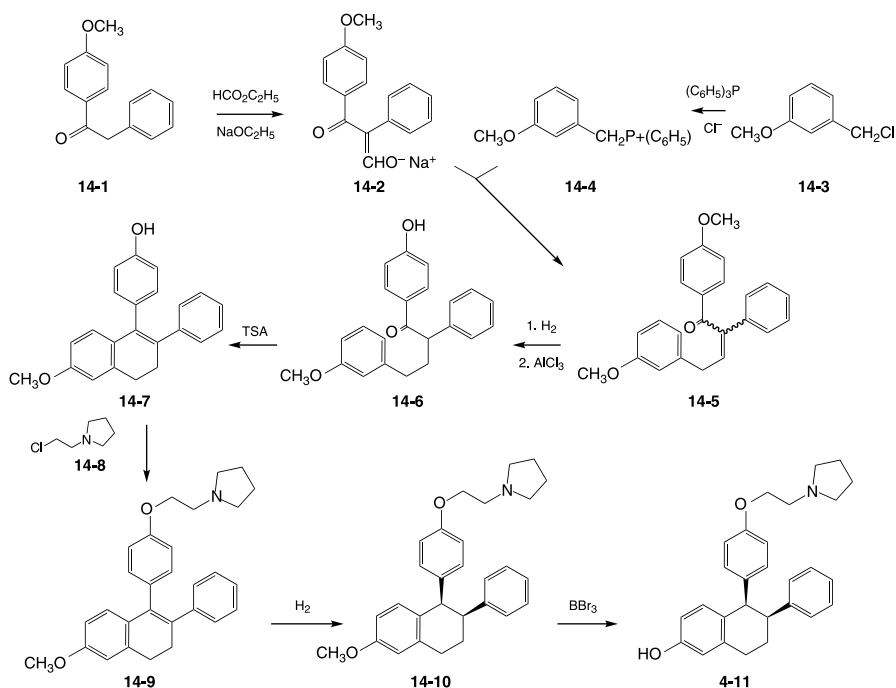
A more recent synthesis for (**14-9**) takes quite a different course. The first step comprises the displacement of one of the halogens in 1,4-dibromobenzene by the alkoxide from *N*-2-hydroxyethylpyrrolidine (**15-2**) in the presence of 18-crown ether to afford (**15-3**). Condensation of the lithium salt from (**15-3**) with 6-methoxy-tetralone (**15-4**) followed by dehydration of the initially formed carbinol give the intermediate (**15-5**), which incorporates the important basic ether. Reaction of that compound with pridinium bromide perbromide leads to the displacement of the vinylic proton by halogen and the formation of bromide (**15-6**). Condensation of that product with phenylboronic acid in the presence of a tetrakistriphenyl-phosphine palladium catalyst leads to the coupling of the phenyl group by the formal displacement of bromine. The product (**14-9**) is then taken on to **lasoxifene** (**14-11**) as above [16].
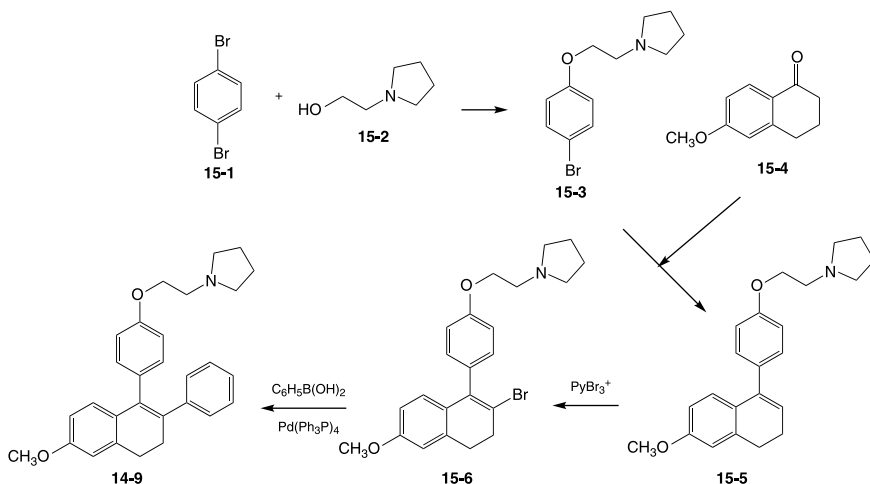
The wide tolerance for structural modification in agonists of the estrogen receptor applies to antagonists as well. The dihydronaphthalene, **trioxifene** (**16-6**), which contains an extra carbonyl group between the ring bearing the basic ether and the bicyclic moiety, retains antiestrogenic activity. Condensation of the enolate from β-tetralone (**16-1**) with ethyl anisoate (**16-2**) leads to the corresponding acylation product (**16-3**), shown here as the more highly conjugated of the two possible enolates. Reaction of that product with the Grignard reagent from 4-anisoyl chloride leads to an attack on the ring ketone ring ketone, which is expected to show more carbonyl character than the exocyclic carbonyl. The first-formed product dehydrates on workup to give the conjugated product (**16-4**). Demethylation by means of the sodium salt of ethyl mercaptan proceeds selectively at the ether *para* to the carbonyl, which is the more electron-deficient of the two (**16-5**). The newly generated free phenol group is then alkylated as its phenolate with *N*-(2-choroethyl)pyrrolidine to afford **trioxifene** (**16-6**) [17].
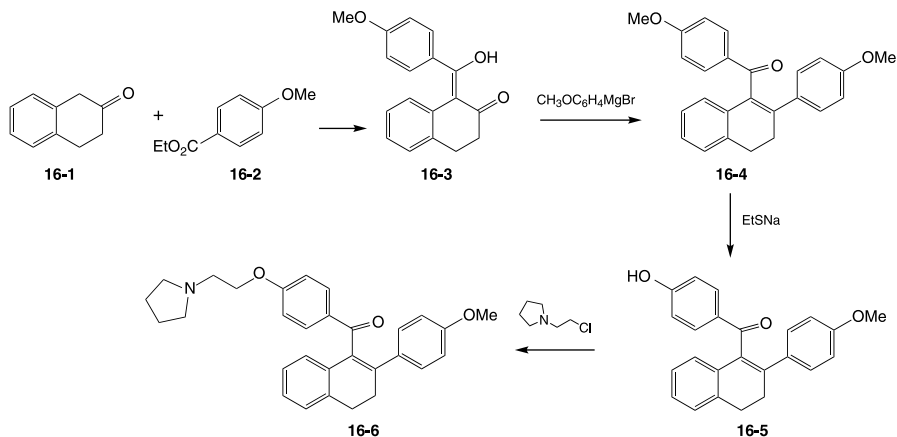
6.2.2.3. Heterocyclic Ethylenes Fused to a Benzene Ring. Replacement of the dihydronaphthalene nucleus by benzothiophene invokes one of the classic bio-isosteric equivalences based on the fact that sulfur is approximately the same size as an ethyl group. The synthesis of this compound starts with the displacement of halogen on phenacyl bromide (**17-2**) by *para*-methoxythiophenoxide (**17-1**) to give the alkylated product (**17-3**). Treatment of that product with polyphosphoric acid (PPA) results in the formation of the 2-anisoyl substituted benzothiophene (**17-5**) rather than the expected 1-anisoyl derivative. The unexpected product can be rationalized by invoking an initial rearrangement of the intermediate (**17-3**) to a thioenol ether such as (**17-4**); Friedel–Crafts cyclization of this will give (**17-5**) directly. The alternative possibility requires 1,2 migration of the anisoyl group from the expected
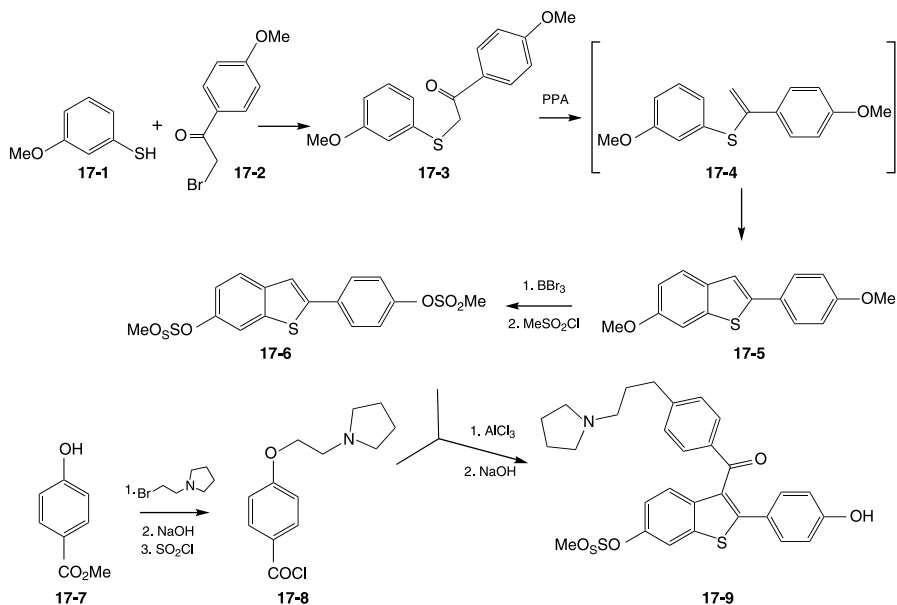
1-anisoyl cyclization product. The methyl ethers are then cleaved by a reagent such as bromine tribromide. Acylation of the thus-freed phenol groups with methanesulfonyl chloride gives the corresponding bismesylate (**17-6**); those protecting groups can be removed under relatively mild conditions. Alkylation of the sodium salt from methyl 4-hydroxybenzoate (**17-7**) with the ubiquitous chloroethylpyrrolidine gives the ester (**17-8**), after removal of the methyl ester with aqueous base. The carboxyl group is then converted to its acid chloride; that is reacted with benzothiophene (**17-6**) in the presence of aluminum chloride to give the 2-acylated derivative. The mesylate groups are then removed by means of a mild base to give the antiestrogen **raloxifene** (**17-9**) [18].

In yet another illustration of the breadth of the SAR (Structure Activity Relations) of estrogen antagonists, the carbonyl group in the estrogen antagonist **raloxifene** can be replaced by ether-oxygen. Reaction of the raloxifene intermediate benzothiophene (**17-5**) with bromine leads to the derivative (**18-1**) halogenated at the 3 position of the thiophene ring. The ring sulfur atom is next oxidized with hydrogen peroxide in order to activate that bromine toward displacement (**18-2**). Reaction of this intermediate with the anion from treatment of the phenol (**18-3**) with sodium hydride displaces bromine and in a single step introduces the ring that caries the requisite basic ether (**18-4**). The sulfoxide function is next reduced to the sulfide oxidation state by means of lithium aluminum hydride. Scission of the methyl ethers with boron tribromide completes the synthesis of the estrogen antagonist **arzoxifene** (**18-5**) [19].
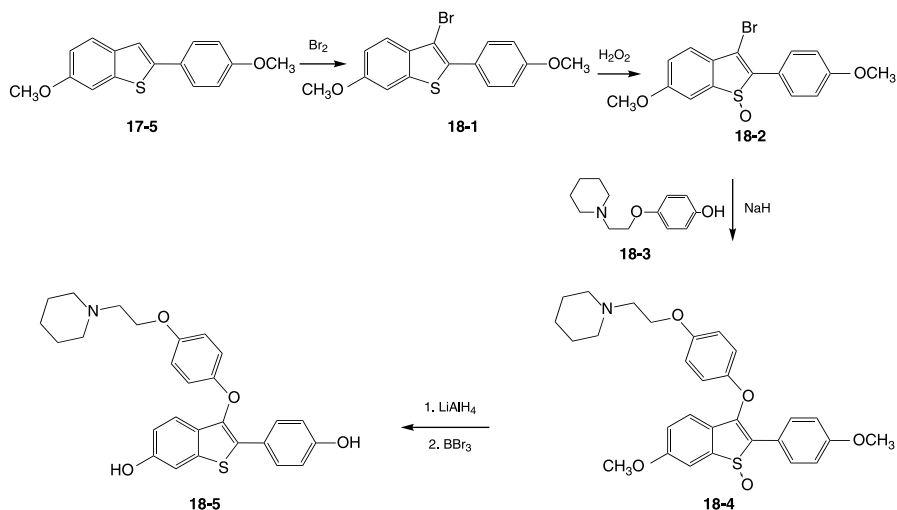
An indole provides the nucleus for the estrogen antagonist **bazedoxifene** (**19-9**). This differs from earlier compounds in not only the ring system but also in the connectivity of the benzene ring that carries the basic ether. The convergent scheme starts with an unusual method for building an indole. Thus, reaction of the aniline (**19-1**) with the bromo acetophenone (**19-2**) in the presence of triethylamine leads to indole (**19-3**) in a single step. The aromatic alkylation step required to close the five-membered ring is likely made possible by the high electron density in that

ring due to the presence of both the ether and the amine functions. Construction of the second ring begins with the alkylation of the phenolic hydroxyl in (**19-4**) with ethyl bromoacetate to give the ether (**19-5**). The benzylic hydroxyl is then replaced by chlorine by means of thionyl chloride. Condensation of the anion from the indole (**19-3**) with the benzylic chloride (**19-6**) introduces the second benzene ring (**19-7**). The ester on the pendant side chain is next reduced to the corresponding alcohol using lithium aluminum hydride. The terminal hydroxyl is then replaced by bromine by reaction with carbon tetrabromide in the presence of triphenylphosphine to afford the intermediate (**19-8**). Alkylation of this last product with azepine completes the construction of the side chain. Catalytic hydrogenation removes the benzyl protecting groups, uncovering the phenolic hydroxyl groups. This affords the estrogen antagonist bazedoxifene (**19-9**) [20].
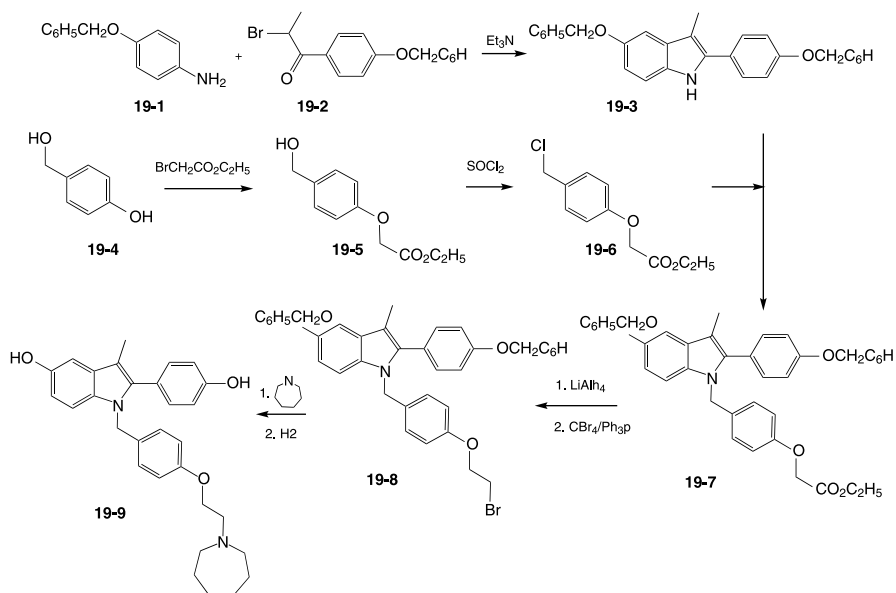
A benzopyran forms the nucleus of the antiestrogen oral contraceptive drug **ormoloxifene** (**20-8**). The preparation starts with straightforward Friedel–Crafts acylation of the monomethyl ether of resorcinol (**20-1**) with the acid chloride from 4-hydroxybenzoic acid (**20-2**) to give the benzophenone (**20-3**). Condensation of that intermediate with phenylacetic acid in acetic anhydride in the presence of triethylamine leads to the formation of coumarin (**20-4**); the overall reaction involves aldol condensation of phenylacetate with the benzophenone carbonyl and esterification of the ortho phenol group; the order in which those steps occur is not clear [21]. Reaction of the coumarin with excess methylmagnesium bromide leads to the addition of two methyl groups to the ester ester carbonyl with a consequent ring opening and the formation of tertiary carbinol (**20-5**). This cyclizes to chromene (**20-6**) on treatment with ethanolic hydrogen chloride, in all likelihood via the carbocation from the loss of the tertiary alcohol. Alkylation of the free phenol group with the familiar chloroethylpyrrolidine gives the

corresponding basic ether (**20-7**). High-pressure hydrogenation of that product leads initially to the expected 3,4-*cis* dihydro derivative; this is equilibrated to the more stable *trans* derivative by treatment with butyl lithium; there is thus obtained **centchroman (20-8)** [22].
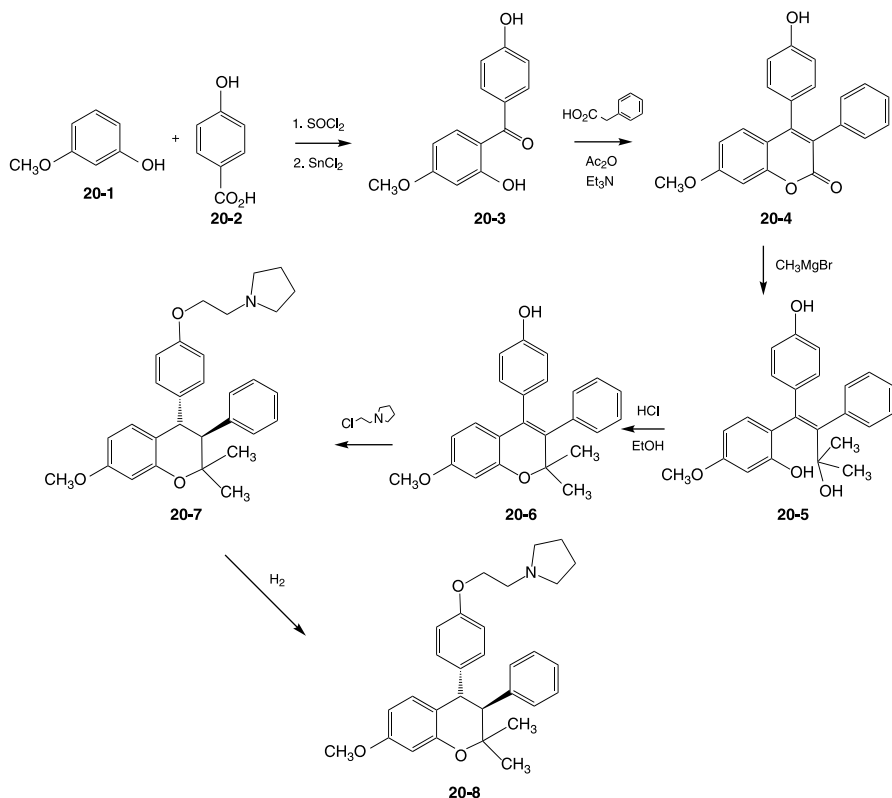
A prominent feature in each of estrogen antagonists noted up to this point consists of pairs of aromatic rings disposed on adjacent positions on either an acyclic ethylene or a fused bicyclic ring system; in the latter cases, one of those rings is positioned next to the ring fusion. These two moieties are present in the antagonist **acolbifene** (**21-10**); the structure of this agent, however, departs from the previous examples by the fact that they occupy the 2,3 rather than the 1,2 position of the bicyclic system. This may account for the report that this agent, unlike its predecessors, is a pure antagonist that, in contrast to its predecessors, shows no partial agonist activity at estrogen receptors. The synthesis of this agent begins with the Friedel–Crafts acylation of resorcinol (**21-1**) with 4-hydroxyphenylacetic acid (**21-2**) to afford the desoxybenzoin (**21-3**). Reaction with dihydropyran leads to the formation of the *bis*-tetrahydro pyrranyl ether (**21-4**); the phenolic group adjacent to the ketone does not react as a result of its chelation with the carbonyl group. Condensation of that intermediate with *para*-hydroxybenzaldehyde (**21-5**) in the presence of piperidine leads initially to the chalcone (**21-6**). The phenol oxygen then adds to the

double bond conjugated with the carbonyl group to afford the benzopyranone (**21-7**). The free phenol group on the newly introduced ring is then alkylated with *N*,4-chloroethylpiperidine to give the basic ether (**21-8**). Reaction of that product with methylmagnesium bromide followed by treatment with acid leads the first-formed alcohol to dehydrate; at the same time the tetrahydopyrranyl groups hydrolyze to reveal the free phenols affording (**21-9**) as a mixture of enantiomers. Separation on a chiral chromatographic column then affords the S isomer **acolbifene** (**21-10**) [23].
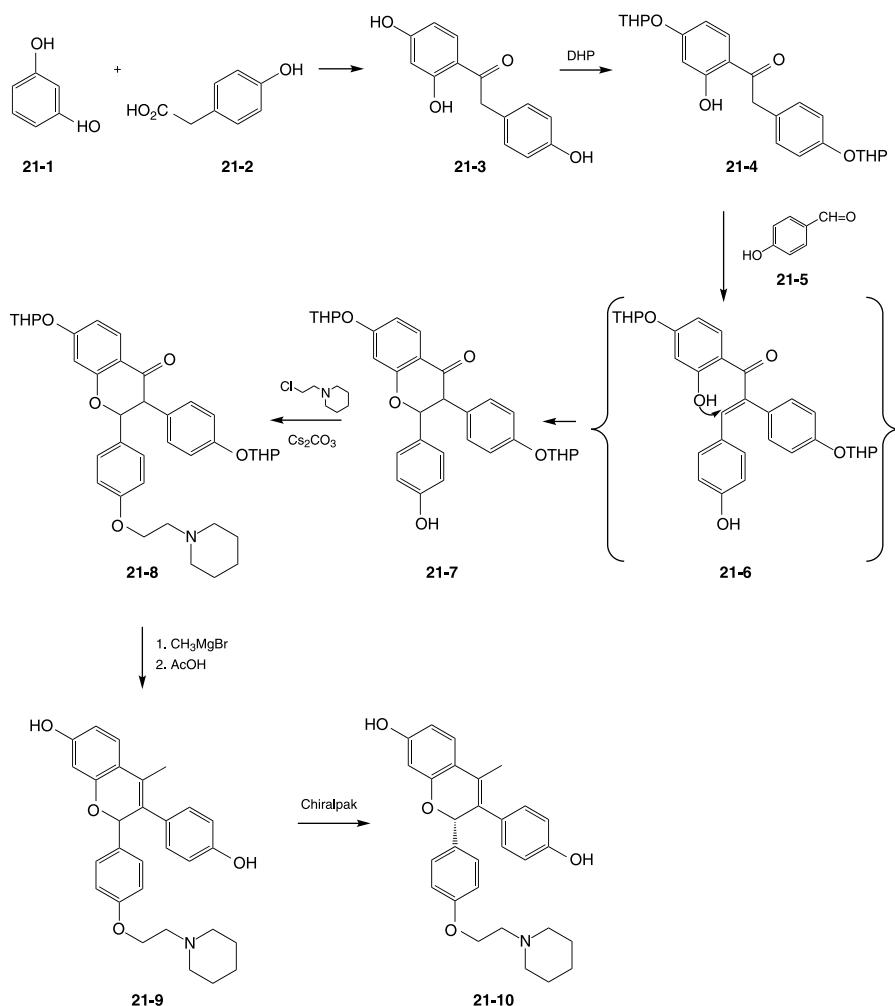
6.2.3. Nonsteroid Androgen Antagonists

Antiandrogens have proven to be very useful in treating benign prostatic hypertrophy, an all too frequent accompaniment of aging. These agents, in addition, have a minor place in the treatment of prostatic cancer. They are also, on a more trivial note, used to

reverse hair loss due to male pattern baldness. Drugs that act as antiandrogens such **finasteride** and **dutasteride** (Chapter 4) generally act by inhibiting the enzyme 5-α-reductase that converts precursors such as testosterone to their active form by reducing the double bond at the 4 position in the steroid A ring. The structures of these drugs, formally derived from steroids, all retain the major part of the precursor nucleus. A pair of more recent, closely related compounds retain the lactam A ring of the steroid-derived agents but replace steroid rings C and D by a simple aromatic ring. These agents retain the 5-α-reductase activity and have as a result been tested in the clinic as potential agents for treating cancer of the prostate. The first step in the synthesis of **bexlosteride** (**22-7**) comprises of conversion of the tetralone (**22-1**) to its enamine (**22-2**) by reaction with pyrrolidine. Reaction of that intermediate with a large excess of acrylamide under carefully controlled conditions leads to the formation of the unsaturated lactam (**22-3**). The sequence can be rationalized by assuming that the first step comprises the conjugate addition to the acrylamide; displacement of the pyrrolidine by amide nitrogen completes the ring formation. The double bond at the ring fusion is next reduced with triethylsilane in the presence of trifluoroacetic acid. There is thus obtained a saturated lactam that consists largely of racemic isomer with the *trans* ring fusion. The amide nitrogen in the product, which still contains a small amount of *cis* isomer, is next alkylated with methyl chloride in the presence of a base (**22-4**). Reaction of that intermediate with methanol opens the lactam ring to yield the corresponding methyl ester (**22-5**); the small amount of *cis* isomer can be separated at this stage since it resists methanolysis. The amino-ester is then resolved via its ditoluyl tartrate salt. Heating the resolved aminoester (**22-6**) with sodium carbonate then regenerates the lactam ring to afford **bexlosteride** (**22-7**) [24].
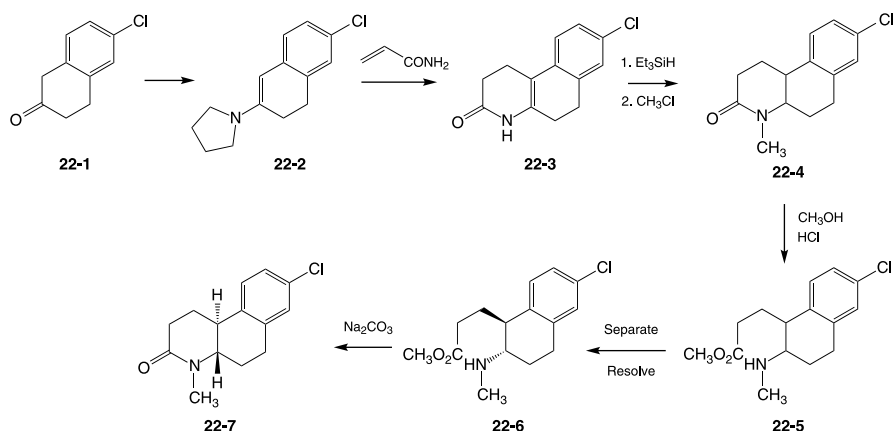
The scheme used to produce a somewhat more complex 5-α-reductase inhibitor relies on a chiral auxiliary to yield the final product as a single enantiomer. The first step in a sequence similar to that above starts with the reaction of bromotetralone (**23-1**) with R-α-phenethyl amine (**23-2**) to afford the enamine (**23-3**). Reaction with methyl iodide adds the methyl group at what will be a steroid-like AB ring junction

(**23-4**). This product is then treated with acryloyl chloride. The initial step in this case probably involves the acylation of nitrogen on the enamine; conjugate addition then completes the formation of the lactam ring (**23-5**). Treatment of that product with triethyl silane then reduces the ring unsaturation and cleaves the benzylic nitrogen bond on the auxiliary to yield (**23-6**) as the optically pure *trans* isomer. Displacement of bromine with the mercapto benzthiazole (**23-7**) completes the synthesis of **izonsteride** (**23-8**) [25].
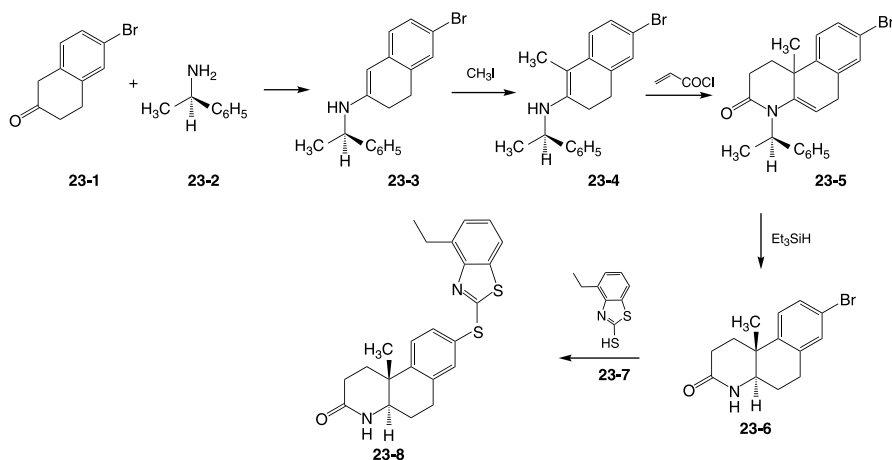
6.2.4. A Nonsteroid Progestin Agonist

The wide structural tolerance of the estrogen receptors has led to the development of the host of nonsteroidal agonists and antagonist described in the prior sections. Nonsteroidal compounds that bind to progestin or receptors have, on the other hand, proven far more elusive, arguably because of the more rigid structural demands at those sites. A benzoxazine has very recently been found to act as a potent agonist at progesterone receptors both *in vitro* and *in vivo*. Molecular modeling suggests that the benzoxazine moiety in this compound fulfills the role of the steroid AB rings while the pyrrole fulfills the role of the D ring in progesterone [25]. Construction of the benzoxazine starts with Grignard reaction of anthranilate (**24-1**) with methyl-magnesium bromide. Treatment of the product (**24-2**) with carbonyl diimidazole closes the oxazole ring (**24-3**). In a convergent scheme, a reaction of N-protected imidazole (**24-4**) with butyl lithium followed by trimethyl borate affords the boric acid derivative (**24-5**). Condensation of this acid with benzoxazole (**24-3**) in the presence of the palladium/triphenylphosphine catalyst affords the coupling product (**24-6**). Treatment of that product with isocyanosulfonyl chloride then adds the required cyano function to the pyrrole (**24-7**). The protecting group on the imidazole is then removed by means of sodium ethoxide. The free amine in (**24-8**) is next methylated by means of methyl iodide in the presence of potassium carbonate (**24-9**). The final step involves the conversion of the carbonyl group to its sulfur

equivalent. Treatment of (**24-9**) with Lawesson reagent from phosphorus sulfide (P_4S_{10}) and anisole then affords the nonsteroidal progestin **tanaproget** (**24-10**) [26].
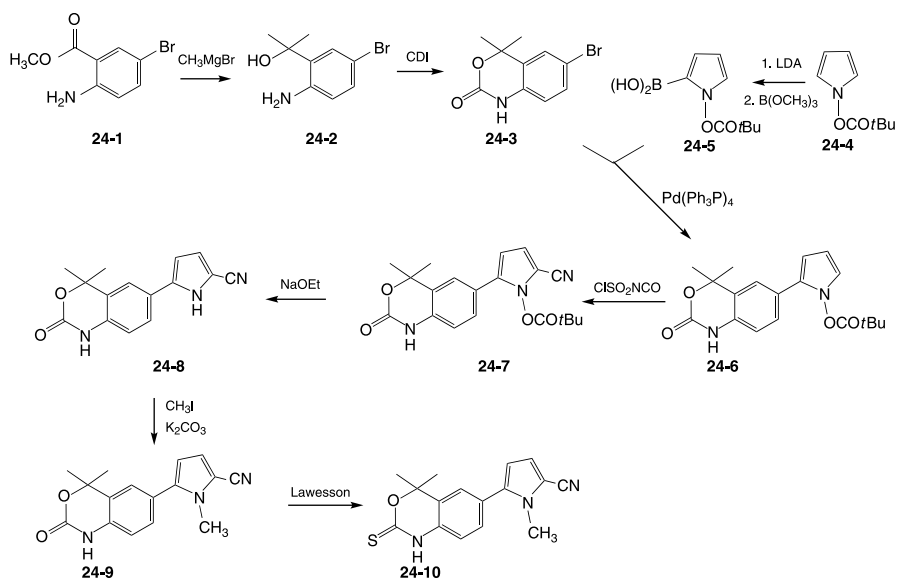
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CHAPTER 7

OPIOID ANALGESICS

7.1. INTRODUCTION

The adventitious discovery, in prehistory, of the analgesic soporific and the euphoriant properties of the dried sap from the flower bulb of the poppy, papaver *somniferum*, has been treated too often elsewhere to warrant repetition. By the nineteenth century organic chemistry had advanced far enough so that the active principle from opium had been isolated, purified, and crystallized. Increasing clinical use of this compound, **morphine** (**1-1**), and its naturally occurring methyl ether **codeine** (**1-2**) disclosed a host of side effects, the most daunting of which was, and still is, these compounds' propensity for inducing physical dependence.

    A modest effort was launched at modifying the compound, even though the detailed structure was still unknown and would remain so for close to another half-century. The product of treating morphine with acetic anhydride is the corresponding diacetate **heroin** (**1-3**), a drug somewhat optimistically originally thought to be less addicting than the parent.

1-1

1-2

1-3
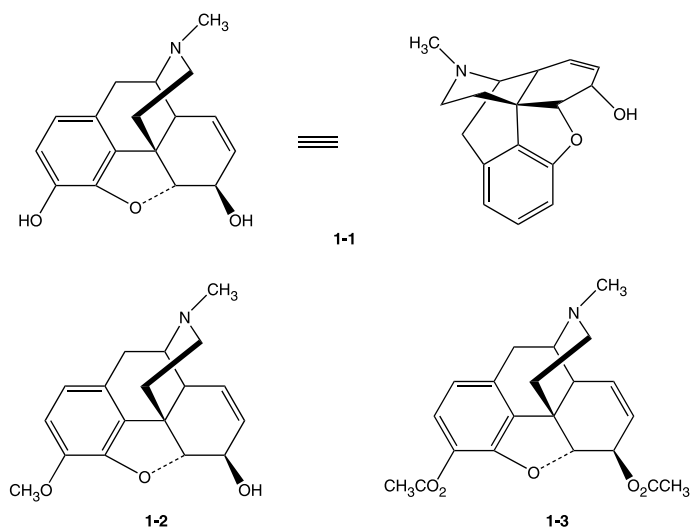
7.2. DRUGS DERIVED FROM MORPHINE

The fact that the structure of morphine was not solved until 1925 [1] severely limited early synthetic work on its derivatives. The relatively early availability of the *N*-demethyl derivative (**3-1**), via Von Braun degradation, did lead to an investigation on the effect on biological activity of substituents on nitrogen. The classical version of this degradation reaction involves treatment of a tertiary *N*-methyl compound with cyanogen bromide. The initial product consists of a quaternary *N*-cyano betaine; internal displacement of the methyl group by the bromide counterion leads to scission of the *N*-methyl bond and loss of methyl bromide with a consequent formation of a cyanamide. This functionality readily hydrolyzes to the secondary amine with the loss of cyanide. A more recent version of this reaction replaces cyanogen bromide with ethyl chloroformate. The reaction follows a very similar sequence; the product of the alkylation–internal displacement sequence, in this case, consists of a urethane. The same secondary amine is obtained on hydrolysis of the initial product.

The *N*-allyl derivative **nalorphine** (**3-2**) is prepared from *N*-demethylmorphine (**3-1**) by alkylation with allyl bromide [2]. The discovery that this compound proved to antagonize the activity of morphine in experimental animals led to the synthesis of the potent opioid antagonist **naloxone** (**8-3**), which is discussed below. Nalorphine (**3-2**), in marked contrast to the latter, does show some modest analgesic activity in humans.

One of the more benign ancillary activities of morphine lies in its activity in suppressing the cough reflex. Catalytic reduction of **codeine** (**1-2**) leads to the dihydro derivative (**4-1**). Oppenauer oxidation of the hydroxyl group leads to **hydrocodone** (**4-2**) [3], a compound used extensively in cough remedies; it is of note, however, that this drug retains considerable opioid activity.

In addition to the shortcomings of morphine (**1-1**) noted above, poor absorption from the GI tract means that it must be administered parenterally. Although the methyl ether codeine (**1-2**) does show oral activity, this derivative does not afford the same measure of analgesia as the parent compound. An analogue methylated on the carbon atom bearing the furan ring combines increased oral and analgesic activities. The key starting material for this derivative, enol acetate (**5-1**), is obtained by treatment of codeine with acetic anhydride. Reaction of (**5-1**) with methylmagnesium bromide leads to the somewhat unusual displacement of the allylic oxygen of the fused furan and the formation of the alkylated product (**5-4**); the stability of the phenoxide anion leaving group may provide some of the driving force for this reaction. Excess reagent presumably reacts with the acyl group without, however, freeing the latent carbonyl group. Bromination of the ketone (**5-2**) proceeds, as expected, on the more highly alkylated carbon to afford bromide (**5-2**). Treatment of (**5-2**) with a base initially leads to the formation of a phenoxide; the anion on oxygen then displaces the adjacent halide to lead to re-closure of the furan ring; cleavage of the methyl ether by means of hydrogen bromide completes the synthesis of **metopon** (**5-4**) [4].

7.3. COMPOUNDS PREPARED FROM THEBAINE

As is often the case with complex natural products, opium, the dried sap from *papaver somniferum*, contains a number of structurally closely related compounds. One of these minor constituents, thebaine (**6-1**), although itself devoid of significant

analgesic activity, incorporates a reactive diene system that has been exploited for preparing several important opioids. This discovery in turn led to the search for strains of the poppy in which this compound predominated; one such strain, *papaver bracteum*, has been reported to yield as much as 26% thebaine from the dried sap of its seed pod.

The product (**6-2**) from the reaction of thebaine with hydrogen peroxide can be viewed as the result from fromal 1,4 addition of two hydroxyl groups across the diene. The perspective depiction of thebaine reveals that the addition in fact occurs at the far more open face of the molecule. The product from this oxidation incorporates a new hydroxyl group at the 14β position and a hemiacetal at the 6 position. Treatment with a mild acid leads to the hydrolysis of this last function and the formation of enone (**6-3**).

Catalytic hydrogenation of the hydrolysis product leads to the orally active compound **oxycodenone** (**7-1**), which is used in a number of analgesic drugs. Cleavage of the methyl ether to the free phenol leads to one of the most potent close analogues of morphine, **oxymorphone** (**7-2**) [5]. Note that both of these compounds carry the hazards of classical opiate dependence liability.

6-3   7-1   7-2
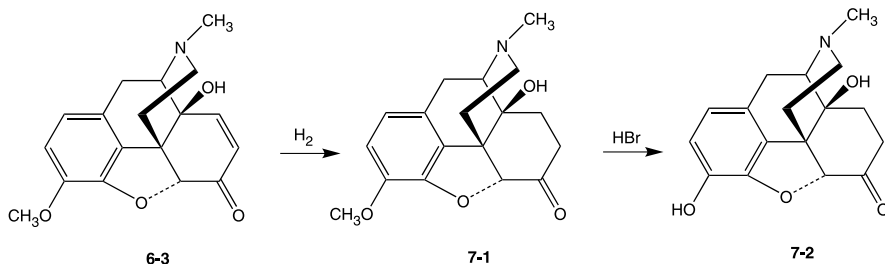
Replacement of the *N*-methyl group in oxymorphone (**7-2**) by allyl provides a potent opiate antagonist. This compound **naloxone** (**8-3**), in contrast to its deoxy analogue nalorphine (**3-2**), is quite devoid of any analgesic or other opiate activity in humans. The drug will in fact precipitate withdrawal symptoms in opiate-dependent individuals. Preparation of the compound begins with protection of (**7-2**) as its acetate (**8-1**). Removal of the methyl group on nitrogen with cyanogen bromide followed by hydrolysis of the first formed cyanamide gives the corresponding secondary amine (**8-2**). Alkylation with allyl bromide and the subsequent saponification of the acetates affords naloxone (**8-3**) [6]. Very small changes in the structure of side chain substituents interestingly lead to compounds that show mixtures of opiate agonist and antagonist activity. Such mixed agonists-antagonists have shown somewhat reduced dependence liability while retaining a good measure of analgesic activity. Thus, the alkylation-saponification on (**8-2**) using 3,3-dimethylallyl bromide gives **nalmexone** (**8-4**) [7]; the use of cyclopropylmethyl bromide leads to **naltrexone** (**8-5**) [8]. This last compound, interestingly, blocks not only opiate receptors but also those involved in the pleasure effects from alcohol consumption. The drug is now approved as a means for treating alcoholics.
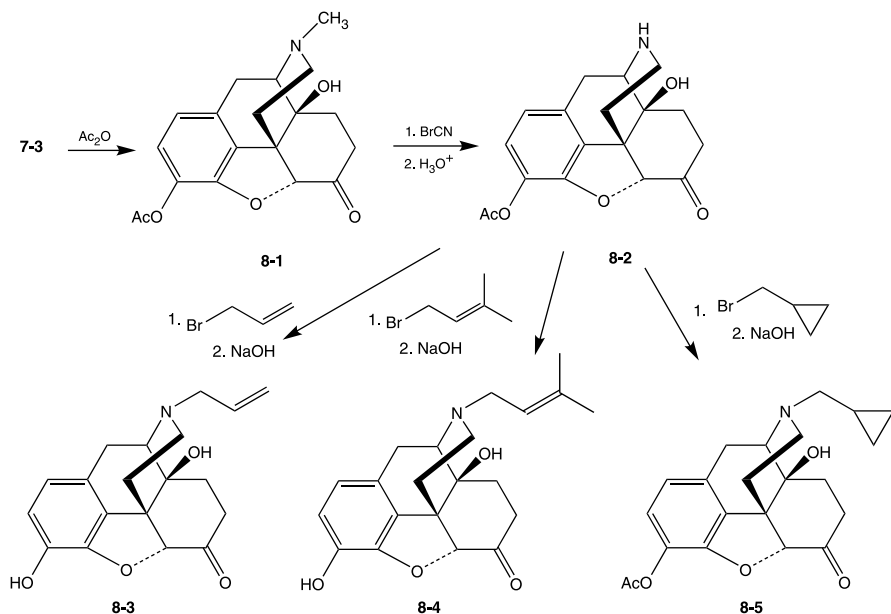
An interesting variation on this theme includes basic nitrogen rather than oxygen at the quaternary 14β position. The first step in this sequence involves the reaction of thebaine (**6-1**) with tetranitromethane in methanol with the overall result of the addition of a nitro group and a methoxyl group across the termini of the diene to form (**9-1**). The reaction can be rationalized by assuming an initial addition of a nitro free radical from decomposition of the reagent. Methanol then quenches the radical left at the opposite end of system. The newly introduced nitro group is then
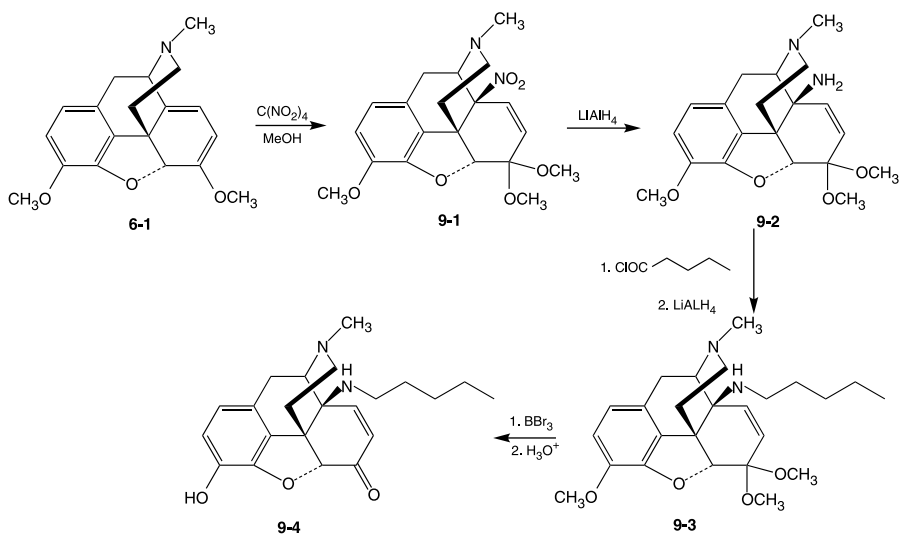
reduced with lithium aluminum hydride to the primary amine (**9-2**). The acetal produced at the 6 position in the addition reaction protects the future carbonyl in the next several steps. The amine is then acylated with valeroyl chloride, and the resulting amide is reduced to an alkyl group, again with lithium aluminum hydride to give (**9-3**). *O*-demethylation with boron tribromide followed by mild acid hydrolysis to remove the acetal affords the opiate analgesic **pentamorphone** (**9-4**) [9].

The diene function in thebaine is of course ideally set up as well for Diels–Alder addition. Condensation of (**6-1**) with methyl vinyl ketone proceeds to give the cycloadduct (**10-1**), with addition proceeding again from the more open face of the molecule. The acetyl side chain occupies the customary endo position on the 2,2,2-bicyclooctyl moiety. The aromatic methyl ether is then cleaved by means of hydrogen bromide. The addition of propylmagnesium bromide to the side chain ketone of this already potent analgesic leads to the tertiary carbinol and **etorphine** (**10-2**) [10]. This extremely active compound is between 1,000 and 10,000 times as potent as morphine as an analgesic *in vivo* in a variety of mammalian species, including humans. The drug is commonly used in flechettes to bring down large game for various studies. A subsequent single injection of naloxone (**8-3**) counteracts the agent and restores the animal to consciousness in a short time.
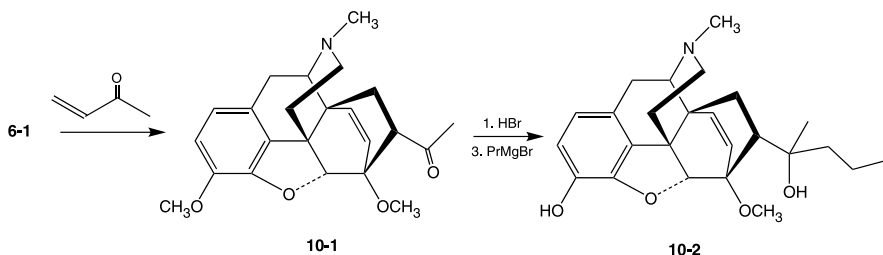
7.4. MORPHINANS

Detailed inspection of the structure of morphine reveals that the backbone of the molecule consists of a reduced phenanthrene ring system [11]. Initial efforts to prepare the compound by total synthesis thus relied on the then-known chemistry used to prepare polynuclear aromatic hydrocarbons; acid catalyzed Friedel–Crafts cyclization played a key role in those approaches. This research culminated in the early 1940s with the successful synthesis by Grewe and his associate, Mondon, of the morphinan (**11-2**) [12], which consists of the bare morphine skeleton. Thus, treatment of benzyl octahydroisoquinoline (**11-1**) with a strong acid leads to the formation of the *bis*-carbocation by successive protonation of the basic nitrogen and then the isolated olefin. Attack of the pendant benzene ring by the resulting carbocation leads to the cyclization and formation of the morphinan. The fact that (**11-2**) showed some modest analgesic activity in animal models demonstrated that the fused furan ring in the natural product could be dispensed with. This finding also led to analogue programs based on this simplified structure.

11-1

11-2
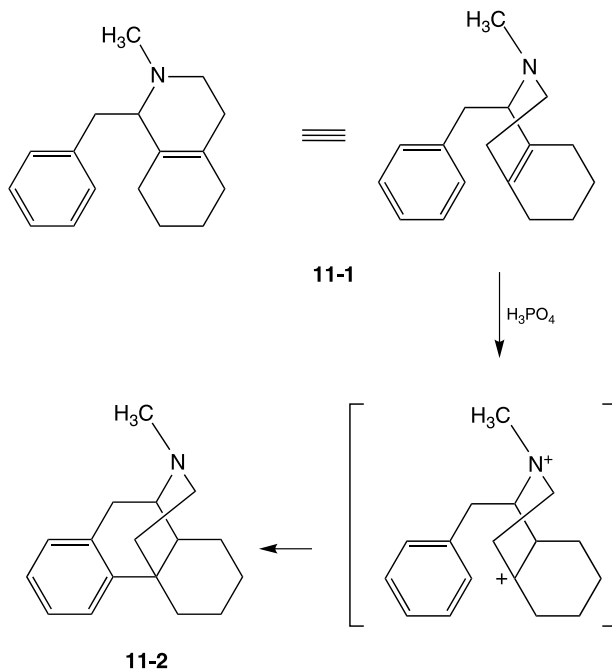
One of the syntheses for a morphinan that has been approved for sale starts by Knoevnagel reaction of cyclohexanone with ethyl cyanoacetate to give a condensation product (**12-1**). Hydrolysis of (**12-1**) leads to the corresponding cyamoacid. The latter loses carbon dioxide under reaction conditions to give (**12-2**); the out-of-conjugation shift of the olefin is a direct consequence of the mechanism of the decarboxylation reaction. Treatment of the nitrile with lithium aluminum hydride then leads to the corresponding primary amine (**12-3**). Acylation of (**12-3**) with p-methoxypenylacetyl chloride (**12-4**) adds the aromatic ring required for the

12-1   **12-2**   **12-3**   **12-4**

12-7   **12-6**   **12-5**
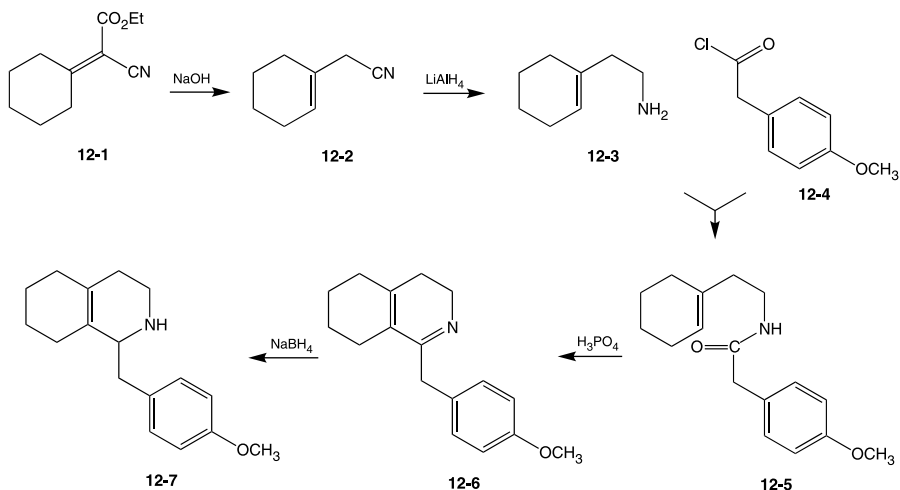
morphinan. The use of the Bischler–Napieralski cyclodehydration of phenylaceta-
mides of arylethylamines comprises one of the standard methods for the synthesis
of dihydroisoquinolines. The reaction works equally well when the benzene ring
involved in the cyclization is replaced by cyclohexene. Thus reaction of (**12-5**)
with phosphoric acid gives the hexahydroisoquinoline (**12-6**) via the enol form of
the amide. Exposure of (**12-6**) to sodium borohydride leads to the selective reduction
of the imine bond and the formation of the morphinan precursor (**12-7**) [13].

Treatment of (**12-7**) with a strong acid proceeds to morphinan (**13-1**) in a manner
quite analogous to the unsubstituted compound. The specific product, which was actu-
ally synthesized some years after the drugs discussed below, has been used to produce a
number of analogues bearing different substituents on nitrogen. Acylation of (**13-1**)
with ethyl chloroformate followed by reduction of the intermediate urethane leads to
the *N*-methyl derivative (**13-2**). Cleavage of the methyl ether then affords the very
potent analgesic drug **racemorphan** (**13-3**) [14]. **Levorphanol**, the levorotatory
isomer obtained by resolution of the racemate [15] or by a scheme that involves
prior resolution of an intermediate, is about six to eight times as potent in humans as
morphine itself. The dextrarotary enantiomer of the *O*-methyl precursor (**13-2**) **dextro-
methorphan** is interestingly quite devoid of analgesic activity. Since this compound
retains antitussive activity comparable to that of morphine, it is found in many
cough remedies. Alkylation of the resolved methyl ether with allyl bromide followed
by cleavage of the methyl ether by means of hydrogen bromide leads to the *N*-allyl
analogue **levallorphan** (**13-4**), a compound that acts largely as an opiate antagonist.
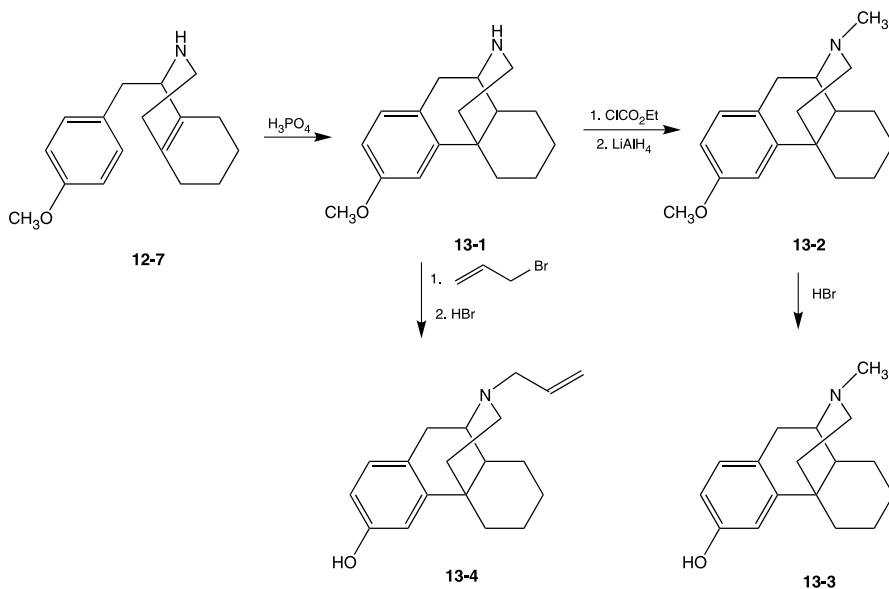
Hydroxylation at the equivalent of the 14 position in morphine has much the
same effect in the morphinan series in that it increases both potency and oral
activity. The somewhat involved synthesis of such a compound begins with the

spirocycloalkylation of 7-methoxy-1-tetralone (**14-1**) with 1,4-dibromobutane to give (**14-2**). Addition of the anion from acetonitrile to the ketone in (**4-2**) gives the tertiary alcohol adduct (**14-3**). The nitrile is then reduced to the corresponding primary amine by means of lithium aluminum hydride to give (**14-4**). The benzylic tertiary hydroxyl eliminates to give a carbocation when treated with a strong acid; this ion then rearranges to the hydrophenathrene (**14-5**).
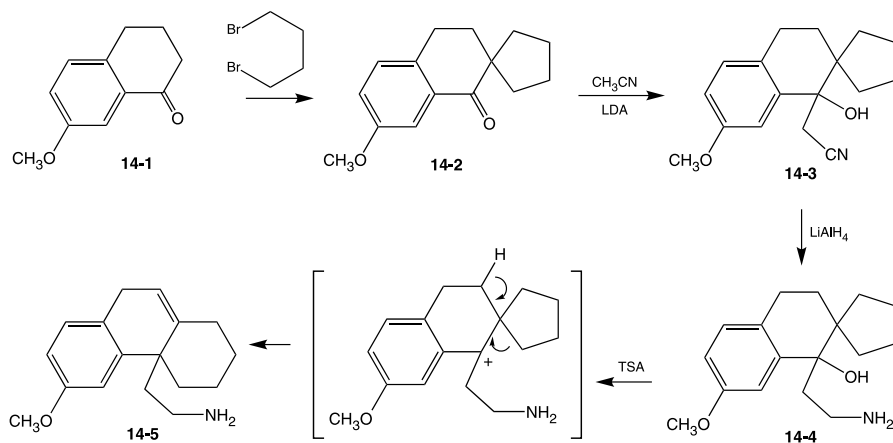
The first step in forming the nitrogen-containing bridging ring involves reaction of the olefin (**14-5**) with bromine. The reaction probably starts by formation of a bromonium ion; a ring opening by the adjacent primary amine leads to (**15-2**) as the hydrobromide salt in which nitrogen occupies the 14 position. Neutralization in the cold frees the still quite basic amine. Basic nitrogen then displaces the remaining bromine to form aziridine (**15-3**). This ring opens on warming to (**15-4**) with a concomitant formation of an olefin at the ring junction; the reaction from (**15-2**) goes directly to this intermediate when carried out warm. The amine is then protected as its trifluoroacetamide by reaction with trifloroacetic anhydride (TFAA) and the olefin is converted to an expoxide with peracetic acid to give (**15-5**); the stereochemistry of the epoxidation results from the fact these morphinans closely resemble thebaine sterically. Reduction of the oxirane by means of lithium aluminum hydride leads to the intermediate (**15-6**).

It is often more advantageous to attach substituents on nitrogen by a two-stage acylation reduction scheme than by direct alkylation, particularly in those cases where alkyl halogen is unreactive or where steric hindrance may interfere. Thus, acylation of (**15-6**) with cyclobutylcarbonyl chloride leads to the amide; reduction using lithium aluminum hydride gives the cyclobutyl derivative **butorphanol** (**15-7**) [16], a mixed–agonist-antagonist analgesic. This drug is interestingly well absorbed through the nasal mucosa. It is currently available as a nasal spray for the treatment of moderate pain.
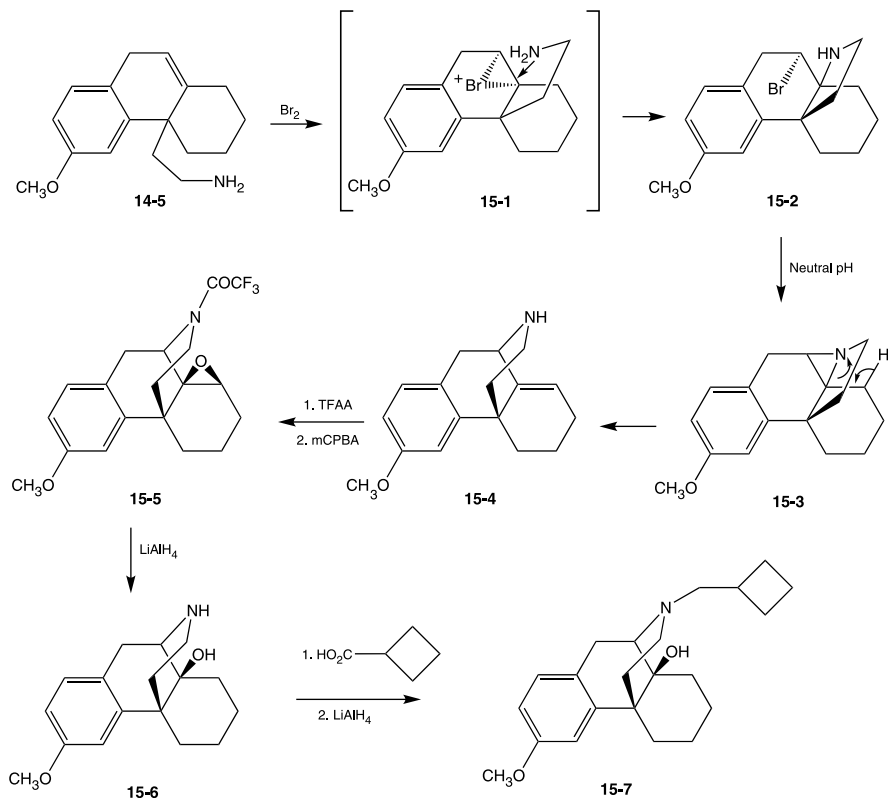
7.5. BENZOMORPHANS

The use of tetrahydropyridines instead of tetrahydroisoquinolines in the Grewe synthesis leads to benzomorphans, which may be viewed as morphine missing both a furan and one alicyclic ring. The fact that the original benzomorphan, which was actually produced by a different synthetic route, showed reasonable analgesic potency, combined with the ready access provided but the Grewe approach, prompted the preparation of a host of analogues [17]. The observation that these compounds seemed to offer few advantages over the accepted central analgesics probably accounts for the fact that a surprisingly small number of these compounds were investigated clinically. The little-known addition of Grignard reagents to ternary imminium salts provides a flexible method for building the two-ring intermediate required for the Grewe-based route. Thus, reaction of *p*-methoxybenzylmagnesium chloride (**16-1**) with the quaternary salt (**16-2**) from reaction of 3,4-lutidine with methyl iodide gives the product (**16-3**) from addition of the organometallic to the ternary imminium function; the reason for the reaction at the more highly hindered position is not immediately apparent.
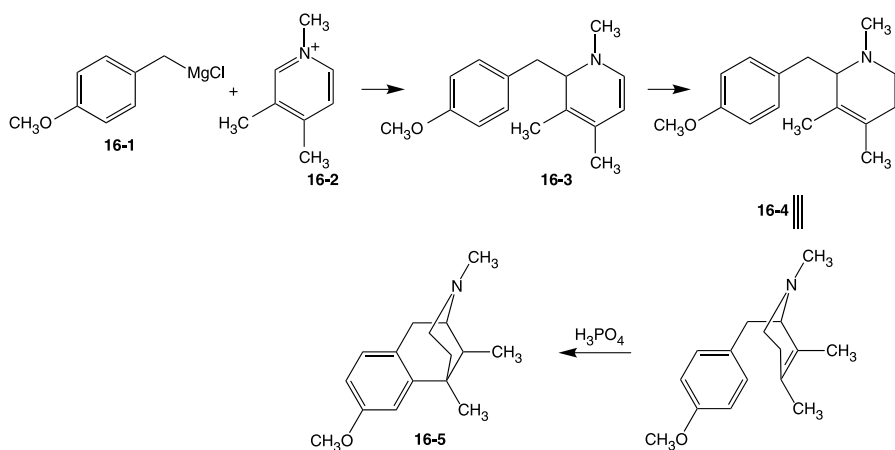
Treatment of (**16-3**) with sodium borohydride leads to the selective reduction of the enamine bond to lead to the tetrahydropyridine (**16-4**). This intermediate undergoes ring closure with a strong acid to give the benzomorphan (**16-5**) in direct analogy to the more complex morphinans. The product consists predominantly of the isomer that bears the equatorial secondary methyl group [18].

Most of the compounds that have been evaluated in greater detail biologically bear more complex side chains on nitrogen. Starting materials are available by an alternative synthesis that leads to intermediates that include unsubstituted piperidine nitrogen. Acylation of the aliphatic amine (**17-1**) with *p*-methoxyphenylacetyl chloride gives the corresponding amide (**17-2**) [19]. Compound (**17-2**) cyclizes to the dihydropyridine (**17-3**) when treated under conditions of the Bischler–Napieralski reaction. Treatment with sodium borohydride results in the reduction of the enamine double bond exactly as above (**17-4**). Cyclization of 60 with a strong acid proceeds to the benzomorphan as in the case of the *N*-methyl analogue. The methyl ether is then cleaved with hydrogen bromide to afford the key intermediate (**17-5**).

Alkylation of (**17-5**) with phenethyl bromide leads to **phenazocine** (**18-1**), a quite potent analgesic that, however, exhibits the same profile of side effects as the classical
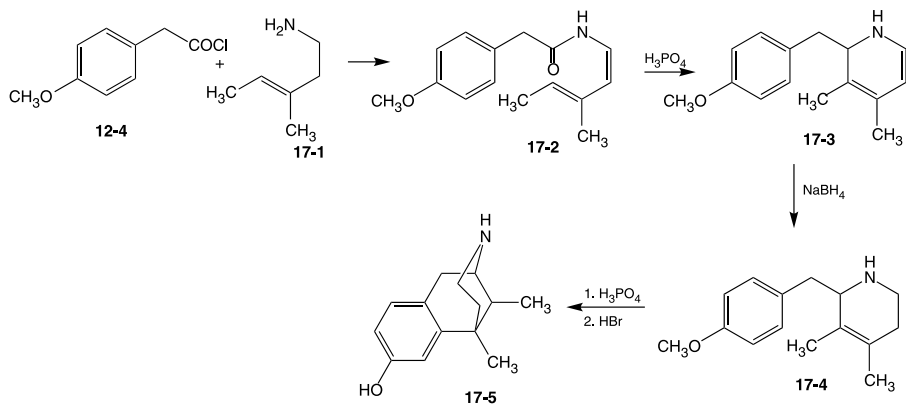
opiates [20]. The 2,2-dimethylallyl **pentazocine** (**18-2**) [21] derivative, on the other hand, shows mixed agonist-antagonist even in humans. The relatively low dependence potential that this drug exhibits has led to its listing by the FDA in the least restrictive category. The cyclopropylmethyl derivative, **cyclazocine** (**18-3**), alternately prepared by the acylation-reduction sequence, has very similar properties; this agent does, however, tend to induce hallucinations.
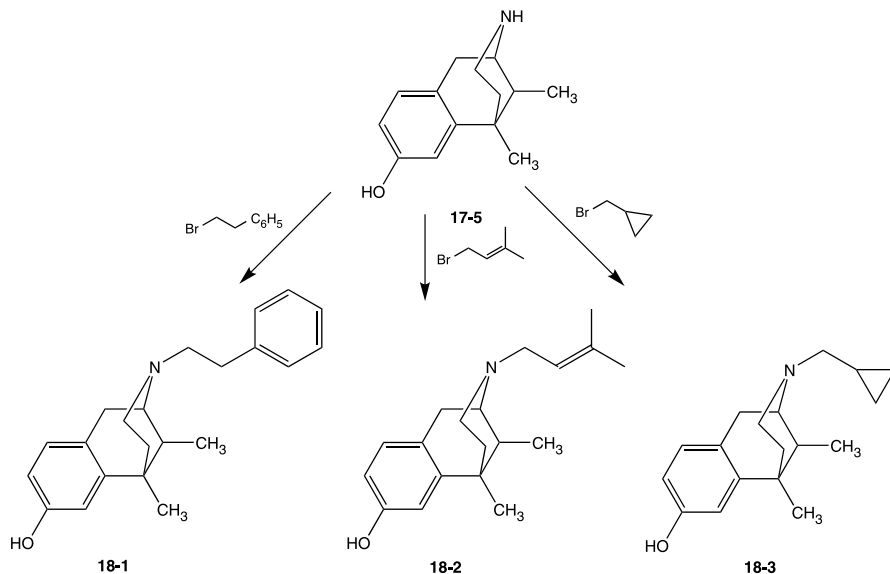
Central analgesic activity is retained when the ring methylene group adjacent to the benzene ring occurs as a carbonyl group. Preparation of **ketazocine** (**19-3**) starts by protection of the amine on the cyclization product (**19-1**) as its acetamide; oxidation with chromium trioxide followed by deprotection leads to the intermediate (**19-2**). Alkylation on nitrogen with bromomethylcyclopropane and the subsequent cleavage of the methyl ether gives (**19-3**) [22]. Ketazocine also exhibits mixed opiate agonist and antagonist activities. Advances in pharmacology led to the discovery several decades ago of receptors that bound opiates. It was found not long afterward that these occurred as several variants. The classical central analgesic agents showed preferential binding to a subcategory named μ (mu after morphine); the function of other variants, such as δ and κ, are still not entirely clear. Ketazocine, for example, was found to have a high affinity for one of the subclasses of opiate receptors. These receptors, designated as κ, take their name from the compound.
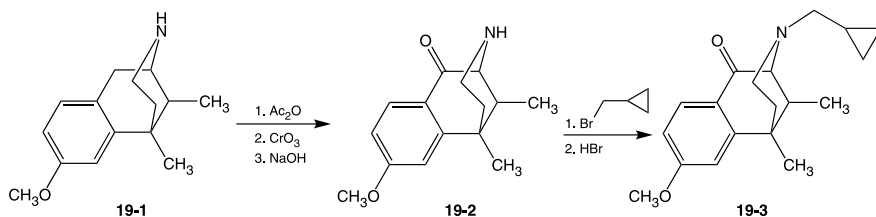
A compound that presents functionality very similar to that of the benzomorphans but with different connectivity is also a central analgesic; the presence of nitrogen as a primary amine is, however, most unusual for an opiate. The bridging ring is in this case constructed by alkylation. Reaction of tetralone (**20-1**) with 1,5-dibromopentane in the presence of two equivalents of sodium hydride leads to the bridged bicyclic ketone (**20-2**); the first alkylation step almost certainly occurs at the more acidic benzylic position, eliminating the possibility of the formation of a spiran at the 3 position. The now highly hindered ketone is converted to its oxime (**20-3**) by reaction with hydroxylamine under forcing conditions. Reduction with hydrogen over Raney nickel takes place largely by approach of the reagent from the more open side away from the bridgehead with the consequent formation of the predominantly all-*cis* isomer (**20-4**). Cleavage of the methyl ether to a free phenol in the ususal manner, followed by resolution, affords the central analgesic **dezocine** (**20-5**) [23].
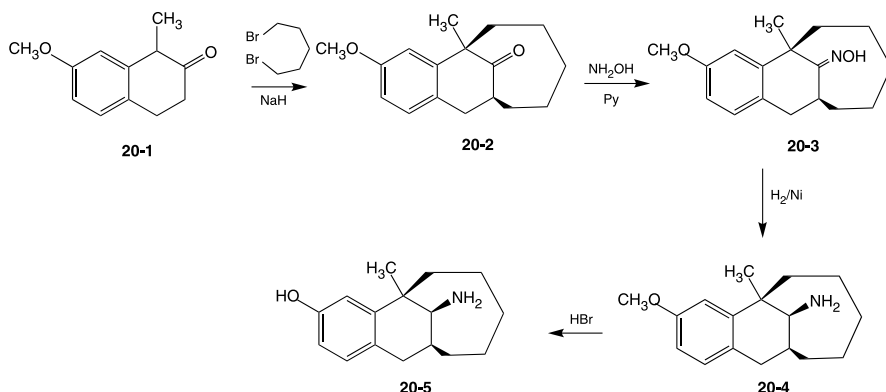
7.6. ANALGESICS BASED ON NONFUSED PIPERIDINES

7.6.1. 4-Arylpiperidines: Meperidine and Its Analogues

Screening of compounds in a broad battery of *in vivo* biological assays without regard to intended activities of those agents, although currently in disfavor, has in fact led to the discovery of a disproportionate number of classes of therapeutic agents. The discovery of yet a further simplification of the minimal opiate analgesic traces back to such an adventitious finding [24]. **Meperidine** (**21-4**), also known as pethidine, retains only two of the rings in morphine, yet it shows full analgesic activity. This compound is still used extensively in the clinic. The key step in one established synthesis of (**21-4**) involves the spiroalkyaltion of the carbanion from phenylacetonitrile (**21-1**) with nitrogen mustard (**21-2**) to afford piperidine (**21-4**); intramolecular alkylation is favored over polymerization because of the enhanced reactivity of the first-formed monoalkylation product. The nitrile is then hydrolyzed with a strong base; the resulting acid is then esterified with ethanolic hydrogen chloride to afford meperidine (**21-4**) [25].

The secondary amine required for the preparation of compounds bearing other substituents on nitrogen could in principle be prepared by *N*-demethylation of

meperidine (**21-4**) itself. A more versatile approach employs the *p*-toluenesulfonyl (Ts) analogue (**21-5**) of the nitrogen mustard; this compound leads to the production of the corresponding piperidine intermediate (**21-6**). Base hydrolysis as above leads to the free acid. Reaction of the acid with ethanolic hydrogen chloride leads to the formation of the ethyl ester with concomitant cleavage of the tosyl amide bond to afford the so-called **normeperidine** (**21-7**). Alkylation on nitrogen with chloroethyl-laniline (**21-8**) leads to **anileridine** (**21-9**) [26], an analgesic that is considerably more potent that its *N*-methyl analogue. The effect on potency of such arylethyl substituents will be revisited below.
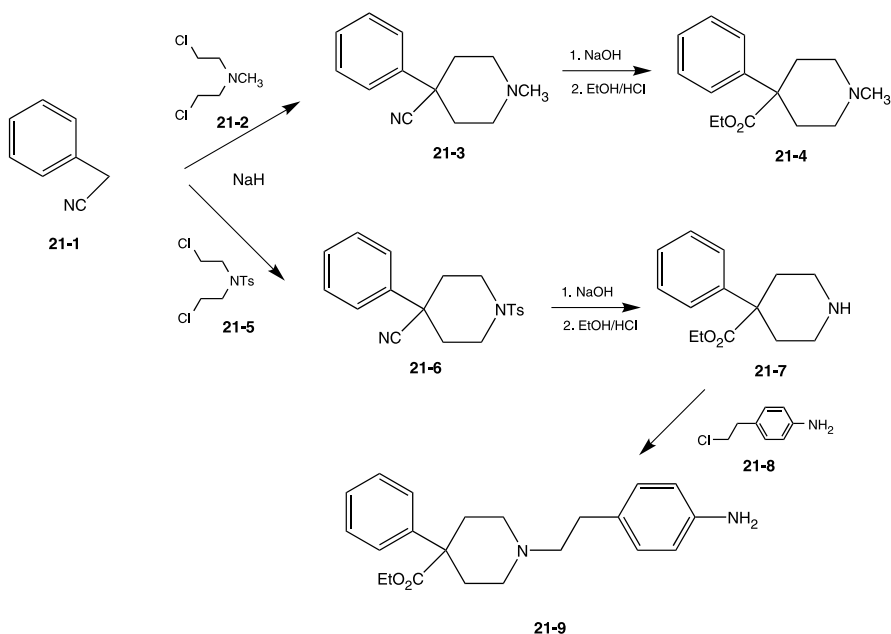
Inhibition of intestinal peristalsis rates among one of the more common effects of morphine that are not directly related to its analgesic activity. The finding that meperidine (**21-4**) shares this effect led to the development of a highly substituted derivative, **diphenoxilate** (**22-3**), that also inhibits intestinal motility and thus acts as an antidiarrheal agent. The side chain in (**22-3**) is prepared by alkylation of the anion from diphenylacetonitrile with 1,2-dibromoethane to give the bromoethyl
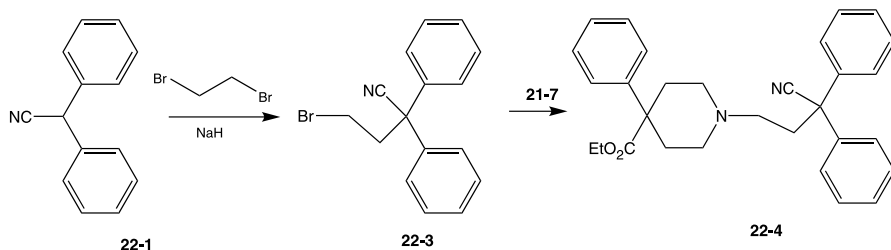
derivative (**22-2**). Reaction of that intermediate with normeperidine (**21-7**) leads to the alkylation of the secondary amine and the formation of diphenoxylate (**22-3**) [27], familiar to world travelers under one of its trade names, Lomotil®.

It will become clear from the next several examples that the carbonyl group in meperidine (**21-4**) acts largely as a bulky presence, since activity is maintained when it is replaced by other space-filling functions. The starting material (**23-1**) for one of those agents can be obtained by spiroalkylation of *m*-methoxyacetonitrile with the nitrogen mustard (**21-2**). The nitrile, in this case, is then condensed with ethylmagnesium bromide; hydrolysis of the first-formed imine with a mild aqueous base gives the corresponding ketone (**23-2**). Standard demethylation of the ether group by means of hydrogen bromide yields the analgesic agent **ketobemidone** (**23-3**) [28].
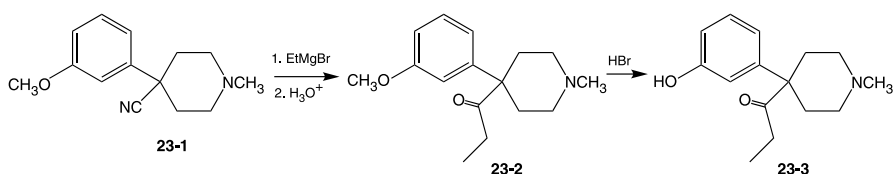
Extensive studies on the SAR of the meperidine (**21-4**) series revealed that incorporation of a methyl group on the ring position adjacent to the carboxyl group markedly increased potency. Both this finding and the fact that the carbethoxy group could be replaced by a function of similar bulk are combined in the design of the analgesic
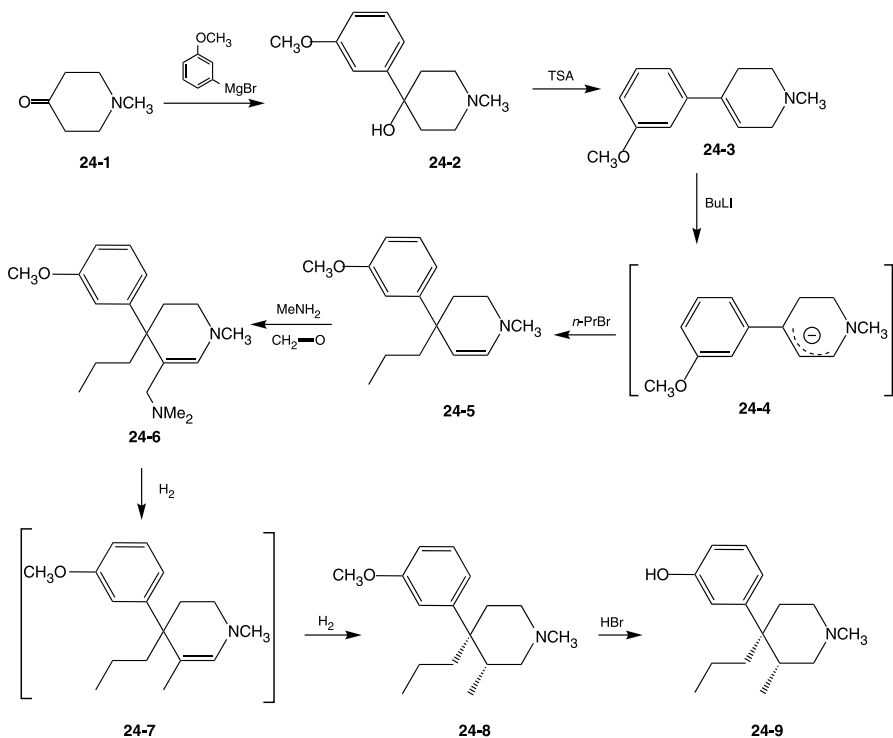
agent **picenadol** (**24-9**). The synthesis of this compound departs significantly from those discussed previously. Thus, in the original route, the required two-ring intermediate (**24-2**) is obtained by condensation of *N*-methyl-4-piperidone (**24-1**) with the Grignard reagent from *m*-methoxybromobenzene. The resulting alcohol (**24-2**) is then dehydrated under acidic conditions to give (**24-3**). Reaction of that intermediate with butyl lithium leads to an ambident anion (**24-4**); treatment of this with propyl bromide leads to alkylation at the more electrophilic terminus of the anion to give the 4-propyl derivative (**24-5**), which, it should be noted, is now an enamine. This function undergoes the Mannich reaction with dimethylamine and formalin to give the corresponding aminomethylated derivative (**24-6**). Catalytic reduction probably proceeds initially to give (**24-7**) from hydrogenolysis of the allylic dimethylamino group. Reduction of the enamine double bond gives a mixture of isomers that consists predominantly of the isomer containing *cis* alkyl groups. The methyl ether is then removed by reaction with hydrogen bromide. Fractional crystallization gives the pure *cis* isomer picenadol (**24-9**) [29].

A significantly shorter method for preparing (**24-9**) hinges on a cuprate-based conjugate addition reaction. Condensation of the ylide from the dimethylphosphonate from bromoacetone with substituted piperidine (**25-1**) yields the conjugated ketone (**25-2**). Reaction of the enone with the cuprate reagent from *m*-methoxybromobenzene proceeds at the terminus of the conjugated ketone to give the intermediate (**25-3**), which contains the required carbon skeleton; **picenadol** (**24-9**) is obtained on exhaustive catalytic reduction of the ketone to a methylene group followed by cleavage of the methyl ether [30].
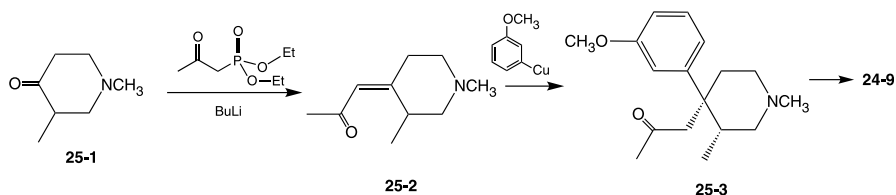
7.6.2. 4-Amidopiperidines: Compounds Related to Fentanyl

All the opiate analgesics discussed thus far incorporated a quaternary carbon removed by two carbon atoms from the basic nitrogen, a structural feature that at one time was considered to be an absolute minimal requirement for activity. Several compounds in which that center consists of a simple acylated secondary amine in fact exhibit considerably enhanced potency over the classical analgesics. The prototype of this class, **fentanyl** (**26-3**), is in fact some 50 times more potent than morphine in humans and as much as 300 times more potent in experimental animal models. This high potency is mirrored by a correspondingly higher binding affinity *in vitro* to μ opiate receptor preparations. There is evidence from the SAR in this and related series that the potentiating effect is due in good part to the presence of the arylethyl side chain on nitrogen. Preparation of the parent molecule begins with the alkyation of 4-piperidone with 2-phenethyl chloride to give the intermediate (**26-1**). Reaction of that product with aniline gives the corresponding Schiff base (**26-2**). Catalytic reduction of the

imine bond followed by acylation of the newly formed secondary amine with propionic anhydride gives fentanyl (**26-3**) [31]. Condensation of the piperidine with *o*-fluoroaniline gives the corresponding Schiff base (**26-4**). The imine in this compound is then reduced as above to a secondary amine; acylation with 2-methoxyacetyl chloride affords the potent analgesic **ocfentanil** (**26-5**) [32].
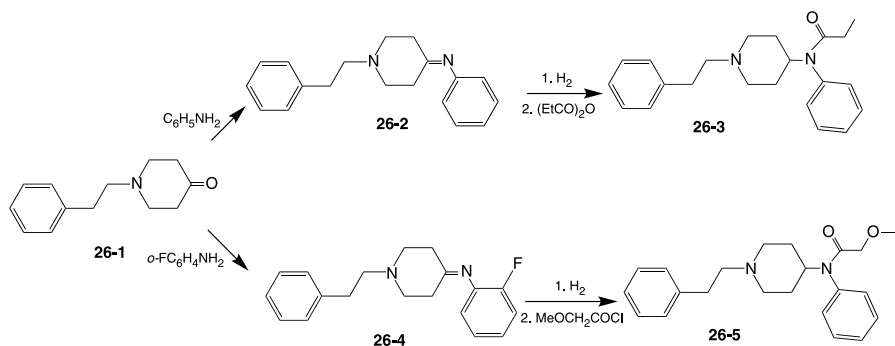
The enhancement of potency due to the presence of an equatorial methyl group noted in the meperidine series also applies to fentanyl analogues. The ring nitrogen of the starting material (**27-1**) for this particular derivative is protected by a benzyl group since it will be replaced later by a somewhat more complex side chain.
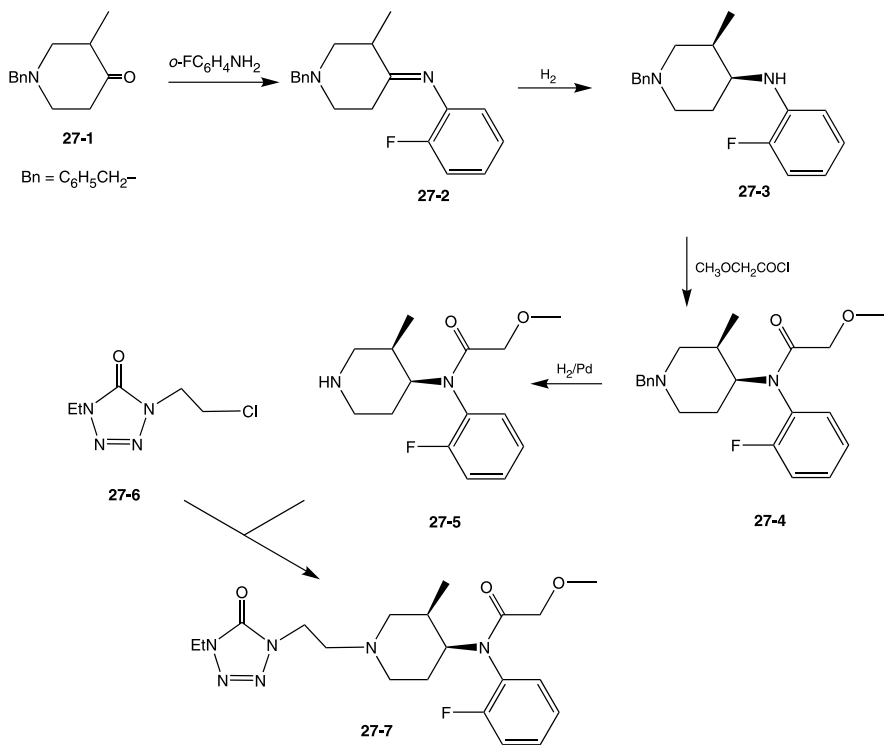
Condensation with *o*-fluoroaniline gives the Schiff base (**27-2**). This compound gives a mixture of *cis* and *trans* isomers (**27-3**) on catalytic reduction. The *cis* isomer is then separated and acylated with 2-methoxyacetyl chloride to give the amide (**27-4**). Hydrogenolysis of the benzyl protecting group then leads to the secondary amine (**27-5**). Reaction with the chloroethyl tetrazolone (**27-6**) leads to the alkylated product and thus **brifentanil** (**27-7**) [33]. The heterocycle in this case acts as a surrogate potentiating aryl group.

Restoring the quaternary center in the fentanyl series results in yet a further enhancement of potency, leading to compounds that show analgesic activity at one-ten-thousandth the dose of morphine in some animal models. The key reaction in the synthesis of these compounds comprises the formation of an α-aminonitrile, a functional group related to cyanohydrins. Thus, reaction of piperidine (**28-1**) with potassium cyanide and aniline hydrochloride leads to the α-aminonitrile (**28-2**). Hydrolysis of the cyano group by means of sulfuric acid affords the corresponding amide (**28-3**); the benzyl group is then removed by hydrogenation over palladium to give the secondary amine (**28-4**). The all-important phenethyl group is then incorporated at the more basic amine with 2-phenethyl chloride to give (**28-5**). Interchange with methanolic hydrogen chloride then converts the amide to a methyl ester; acylation of the secondary amine with propionic anhydride affords **carfentanil** (**28-6**) [34]. The potentiating effect of a ring methyl group obtains here as well; the analogous sequence starting with 3-methyl piperidine (**27-1**) leads to **lofentanil** (**28-7**) [35].
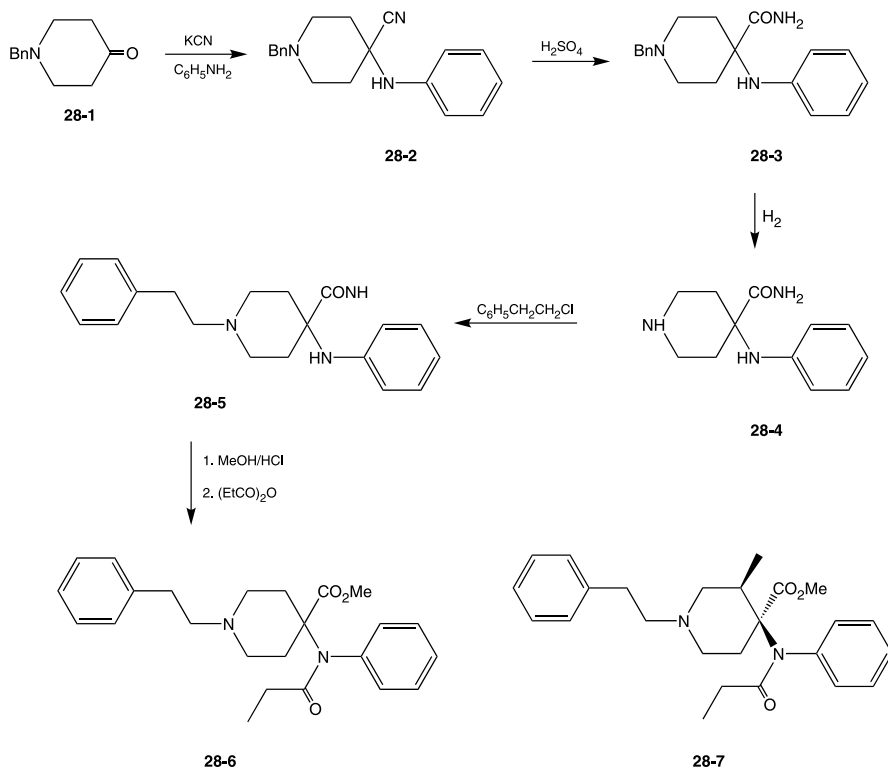
The exact nature of the carbon substituent on the quaternary center, as in the meper-idine series, is apparently not critical for good potency. Replacement of the ester by a methoxymethyl group removes the site for metabolic inactivation of the drugs by serum esterases. Alkylation of the ring nitrogen of the secondary amine (**28-4**) with 2-chloroethylthiophene (**29-1**) gives the intermediate (**29-2**). The amide is then converted to an ester (**29-3**) as above by an interchange reaction. Reduction of the ester in (**29-2**) by means of lithium aluminum hydride converts that group to the cor-responding carbinol (**29-4**). The alkoxide from the hydroxyl is then alkylated with methyl iodide to give methyl ether (**29-5**). Acylation of the aniline nitrogen with pro-pionic anhydride completes the synthesis of **sufentanil** (**29-6**) [36].
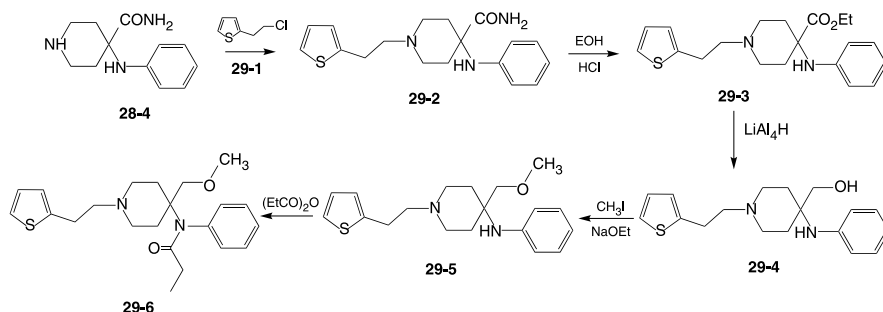
As alluded to in the preceding paragraph, the design of drugs that would be protected against metabolic inactivation has been a long-term preoccupation in medicinal chemistry. The reverse concept, drugs that contain deliberate metabolic weak links so that blood levels of parenteral agents can be quickly dropped, is of much more recent origin. The β-blocker **esmolol** represents one of the pioneer
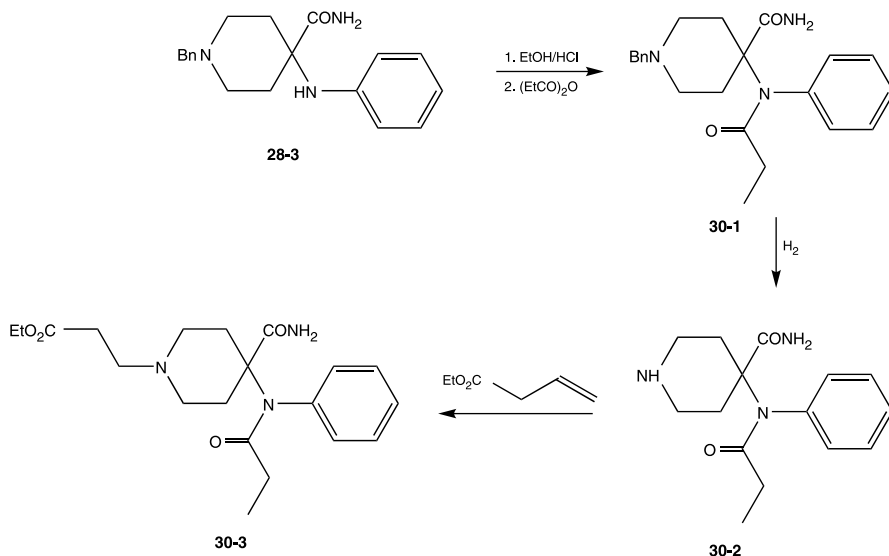
efforts in this area (see Chapter 2). This concept has been applied to opiates as well by the design of an agent with a terminal ester on the side chain on the ring nitrogen. The carboxylic acid product from the interaction with serum esterases will presumably not cross the blood–brain barrier and consequently not reach central opiate receptors. Preparation of the compound based on this rationale begins with the amide-ester interchange of the *N*-benzylpiperidone derived intermediate (**28-3**); acylation with propionic anhydride gives amide (**30-1**). The benzyl protecting group is then removed by hydrogenation over palladium (**30-2**). Michael addition of the secondary piperidine nitrogen to ethyl acrylate provides the weak link–containing side chain. There is thus obtained **remifentanil** (**30-3**) [37].

Ileus, that is, paralysis of the gastrointestinal tract, is a common side effect from surgery. The shock of the operation accompanied by heavy use of opiates shuts down intestinal peristalsis. The structure of a drug to treat ileus in effect comprises a very potent synthetic opiate modified by a polar glycine residue. That fragment is designed to keep the drug out of the CNS thus abolishing its activity as a central analgesic. Activity on peripheral sites, however, persists. Reversing post-operative ileus comprises one of the main applications of this compound. The synthesis of this compound starts with the addition of the Grignard reagent from substituted bromobenzene (**30-1**) to piperidone (**31-2**). The newly formed hydroxyl group in (**31-3**) is then acylated with ethyl chloroformate (**31-4**). Heating the resulting ester (**31-4**) leads to the formation of the styrene (**31-5**). Treatment with a base under equilibrium
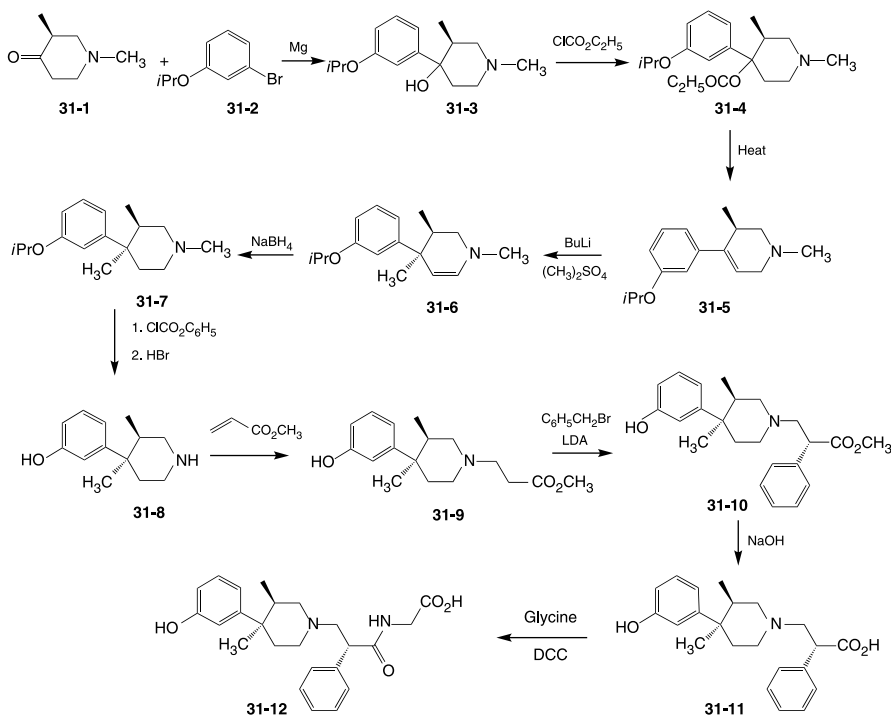
conditions leads to the migration of the negative charge to the quaternary carbon adjacent to the aromatic ring. The addition of dimethyl sulfate thus leads to alkylation at that position (**31-6**). Reaction with sodium borohydride leads to a reduction of what is now an enamine and thus the formation of the saturated piperidine (**31-7**). The methyl group is then removed using chloroformate in the modern version of the Von Braun reaction. Treatment of the product (**31-8**) with methyl acrylate leads to Michael addition and the formation of (**31-9**). The carbon adjacent to the ester is next converted to its enolate with lithium diisopropyl amine; the addition of benzyl bromide leads to the alkylation and formation of (**31-10**). The ester is then saponified. Condensation with glycine ester followed by saponification then gives **alvimopan** (**31-12**) [38].

7.6.3. Miscellaneous Compounds

7.6.3.1. 1,2-Bisaminoceclohexanes.
Several compounds in which the basic nitrogen present in the piperidine analgesics is moved out from the ring have been investigated in some detail. This research indicated that these agents bind largely to κ-opioid receptors. Though they show good analgesic activity in various animal models, this activity does not extend to humans, where they show very disappointingly poor efficacy. The synthesis of the first of these, **spiradoline (32-13)**, begins with the addition of the lithio reagent from the treatment of ethoxyethyl with butyl lithium to the monoacetal (**32-2**) of cylcohexa-1,4-dione. The ether is then cleaved, for example, with hydrogen bromide (**32-3**). Exposure of that intermediate to an aprotic strong acid probably leads first to the loss of the tertiary carbinol. The remaining hydroxyl group then adds to the resulting carbocation to form the cyclic ether (**32-4**). Cleavage of the cyclic acetal leads to the corresponding ketone (**32-5**). This

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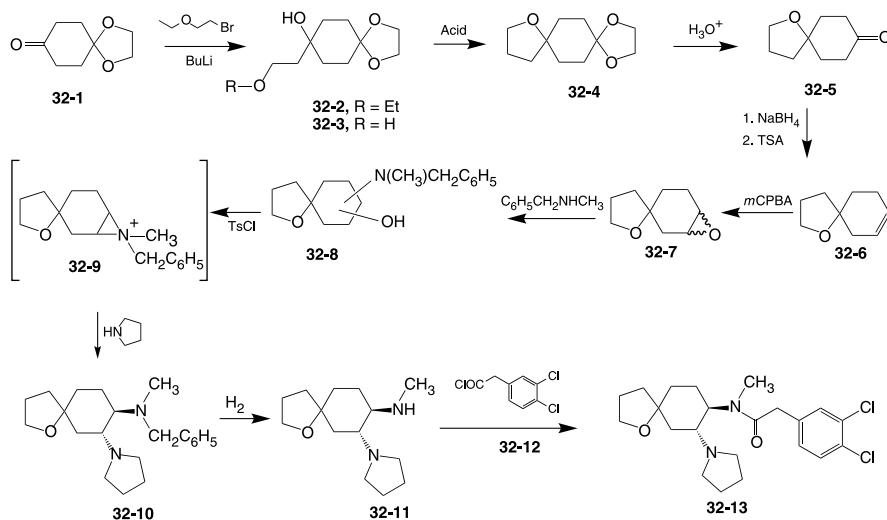
function is then reduced to an alcohol and dehydrated by means of a strong acid (**32-6**). The newly introduced olefin is then treated with peracid to afford an epoxide (**32-7**) of undetermined stereochemistry. The sequence of steps that follow is intended to transform that function to a *trans* vicinal diamine. Reaction of the epoxide with benzylmethylamine leads to a mixture of amino alcohols (**32-8**). Reaction of the mixture with tosyl chloride initially converts the hydroxyl group to a chloride; the halogen is then displaced by the adjacent amine to form an aziridinium salt such as (**32-9**). Exposure of that reactive intermediate to pyrrolidine leads to ring opening to the *trans* diamine (**32-10**). Catalytic reduction then cleaves off the benzylamine to afford the secondary amine (**32-11**). Acylation of that amine with 3,4-dichlorophenylacetyl chloride (**32-12**) affords the amide and thus spiradoline (**32-13**) [39].

A benzofuran group replaces the dichlorophenyl moiety in (**32-13**) in the κ-opioid ligand **enadoline**. The synthesis starts with the oxidation of the xylenol methyl ether (**33-1**) with potassium persulfate; the reactions proceeds at the methyl group adjacent to the ether to afford the corresponding benzyl alcohol. Reaction with manganese dioxide then affords the salicylaldehyde (**33-2**). Alkyationf of the phenol with diethyl bromomalonate probably proceeds to afford initially the product of *O*-alkyation (**33-3**); in the presence of excess base the enolate goes on to add to the adjacent aldehyde to give the benzofuran (**33-4**); this intermediate then decarboethoxyalates to afford the observe product, benzofuran (**33-5**). The next several steps involve the conversion of the methyl group to an acetic acid. Thus, halogenation with *N*-chlorosuccinimide followed by treatment of the benzyl chloride intermediate with a base leads to the alcohol; the ester is saponified in the process to yield (**33-6**). Heating the hydroxy-acid in quinoline in the presence of copper powder leads to the loss of the carboxylate carbon to afford (**33-7**). Reaction of this last product with *N*-chlorosuccinimide
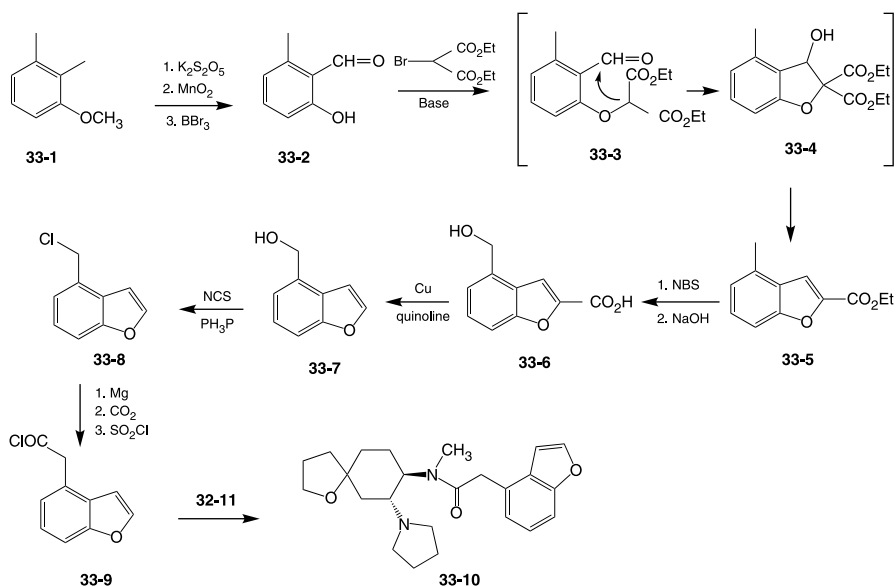
in the presence of triphenylphosphine converts the benzylic hydroxyl group to the corresponding chloride (**33-9**). The Grignard reagent from the reaction of (**33-9**) with magnesium is then allowed to react with carbon dioxide to afford the carboxylic acid; thionyl chloride then yields the requisite acid chloride. This product is then used to acylate the diamine intermediate (**32-11**) in the synthesis of spiradoline. There is thus obtained the κ-ligand **enadoline** (**33-11**) [40].

7.6.3.2. Open Chain Compounds. An open chain version of the "adolines" (**32-11, 33-11**) also binds quite selectively to κ-opiate receptors. This agent, too, shows little if any central analgesic activity and is under investigation for the treatment of irritable bowel syndrome. One enantiospecific synthesis starts with the formamide derivative (**34-1**) of (2*S*)phenylalanine. Reaction of 3(*S*)-hydroxypyrrolidine (**34-2**) with the acid chloride from the reaction of the acid with ethyl chloroformate leads to the *bis*-amide (**34-3**). Treatment of that intermediate with lithium aluminum hydride results in the reduction of both amide groups to give the diamine (**34-4**). The coupling of (**34-4**) with the acid chloride (**34-5**) from diphenylacetic acid leads to the formation of the corresponding amide and thus **asimadoline** (**34-6**).
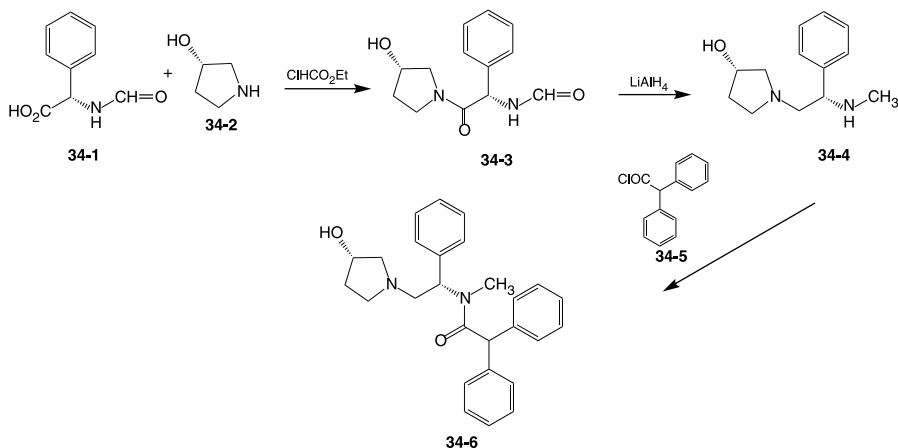
A compound that incorporates some of the structural features that were at one time believed to be essential for analgesic activity binds to sigma opiate sigma receptors, a subclass not associated with pain pathways. This compound thus has no analgesic activity; it has, however, found use as an antidepressant. Alkylation of the anion from 2-phenylbutyric acid (**35-1**) with the allylic halide (**35-2**) gives the acid (**35-3**). In an Arndt–Eistert sequence, the carboxylic acid is converted to the corresponding azide by reaction in turn with thionyl chloride and sodium azide. Heating the azide (**35-4**) in an aprotic solvent then affords the isocyanate rearrangement product (**35-5**). Reduction with lithium aluminum hydride gives the *N*-methylamine (**35-6**). This is then acylated with the acid chloride from cyclopropyl carboxylic acid to give the amide (**35-7**). Reduction of the amide, again with hydride, gives the antidepressant **igmesine** (**35-8**) [41].
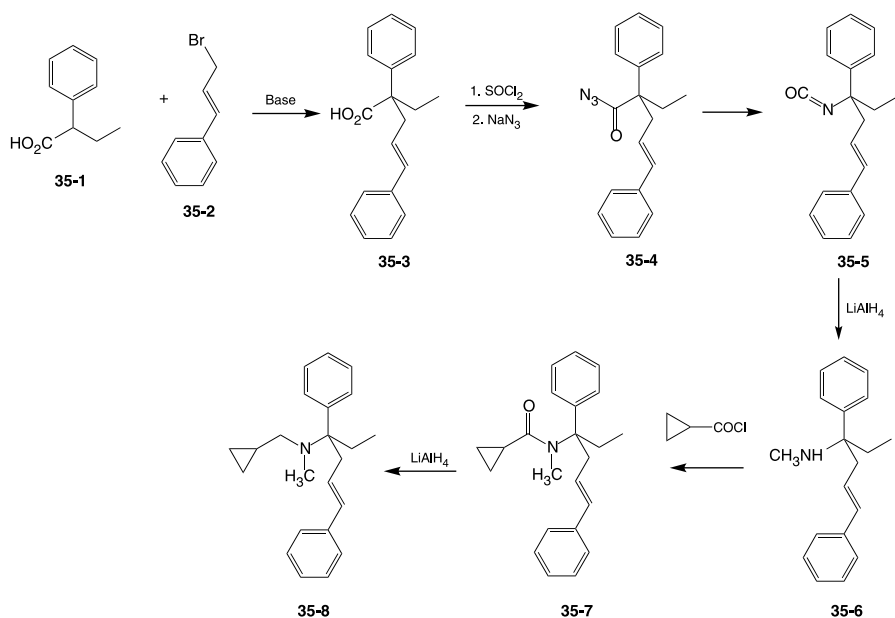
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CHAPTER 8

DRUGS BASED ON FIVE-MEMBERED HETEROCYCLES

8.1. INTRODUCTION

Well over half of all therapeutic agents contain heterocyclic rings. In many cases those fragments comprise the very core of the active moiety or pharmacophore. The antibiotic activity of the cephalosporin antibiotics, as an example, is clearly attributable to the presence of the fused azetidone ring, while the anxiolytic activity of the benzodiazepines can be traced to the aryl fused diazepine ring present in those drugs. Examples discussed in this chapter and those that follow have been chosen on the basis that either their heterocyclic component is believed to form part of a pharmacophore or that they alternatively illustrate aspects of the chemistry of particular heterocyclic ring systems. In a large number of drugs, however, the heterocyclic component is in fact a surrogate for an open chain amine, as illustrated by those drugs bearing piperidine or pyrrolidine rings in lieu of open chain tertiary amines. Discussions of such compounds will, as a rule, be found in earlier chapters.

8.2. RINGS THAT CONTAIN ONE HETEROATOM

8.2.1. Furans

Virtually all drugs that contain a furan ring involve starting materials in which the ring is preformed. A sizeable number of antibacterial agents were at one time available that were based on relatively simple derivatives of 5-nitrofuran. These have greatly

diminished in importance due to the discovery of side effects and, more importantly, the availability of safer and more effective antibacterials. **Nitrofurazone** (**1-2**) and its more hydrophilic congener **nidroxyzone** (**1-4**) are typical of some of those drugs. The former is prepared by reaction of 5-nitrofuran with the semicarbazone (**1-3**) while its analogue results from condensation of the aldehyde with the carbamide from 2-hydrazinoethanol [1].
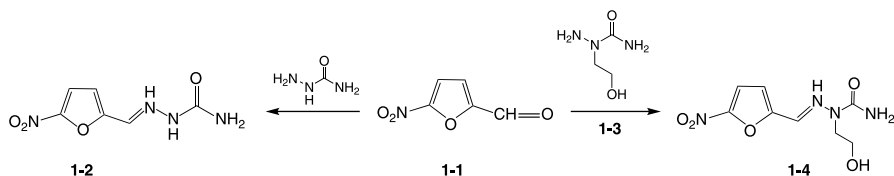
The imine function is replaced by a carbon to carbon double bond in a somewhat more complex nitrofuran antibacterial agent. Condensation 5-nitrofurfuraldehyde with the carbanion obtained by treating 2,6-lutidine (**2-1**) with a strong base affords the diarylethylene (**2-2**) of unstated stereochemistry (shown as *trans* for aesthetics reasons). Oxidation of the remaining pyridil methyl group starts by reaction of the product (**2-2**) with a peracid to give the corresponding *N*-oxide (**2-3**). Treatment of the intermediate with acetic anhydride leads initially to the formation of a transient dehydro *O*-acetate (**2-4**); the acyl group then undergoes O to C migration with consequent bond reorganization; the overall result of this version of the Polonovski is the formation of the acetate (**2-5**). Saponification then yields the final product, **nifurpirinol** (**2-6**) [2].
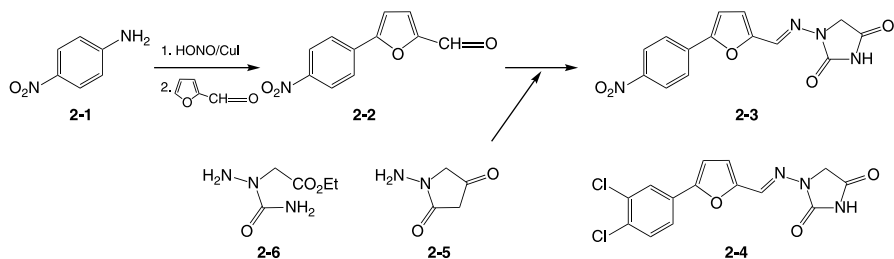
The side chain for furan derivatives yet further removed structurally from the nitrofurans is obtained by internal amide-ester interchange of the *N*-aminoglycine derivative (**3-6**) with resulting cyclization to the imidazolinedione derivative (**3-5**). Cuprous
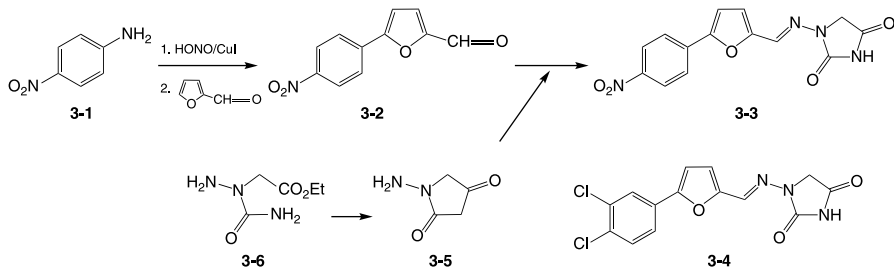
chloride catalyzed coupling of the diazonium salt from *p*-nitroaniline (**3-1**) and furfural leads to the 5-nitrophenyl furan derivative (**3-2**). Reaction of the aldehyde group in this last intermediate with hydrazine (**3-5**) leads to **dantrolene** (**3-3**), a compound that now exhibits muscle relaxant rather than antibacterial activity [3]. Replacement of the 4-nitro group in (**3-1**), a group that may have traced conceptually to the antibacterial furans, by 3,4-dichloroaniline retains muscle relaxant activity. This compound, **clodanolene** (**3-4**), is prepared by the same sequence starting instead with 3,4-dichloroaniline [3].

An imidazole ring provided the nucleus for the first of the antiulcer drugs that act by blocking histamine H_2 receptors, **cimetidine** (**64-3**). The presence of this hetero-cyclic ring, as will be discussed later in this chapter, traces back to the occurrence of that moiety in the normal agonist for the receptor, histamine. Replacement of the ring by furan, in conjunction with some rearrangement of the functionality, leads to the very widely used histamine H_2 receptor blocker, **ranitidine** (**4-5**) [4]. The first step in the synthesis consists of adding a dimethylaminomethyl group to furfuryl alcohol (**4-1**) by Mannich reaction with dimethylamine and formalin to give (**4-2**). Treatment with thio-2-aminoethylthiol in the presence of hydrogen chloride leads to the displacement of hydroxyl by the thiol and the formation of thioether (**4-3**), a reaction that probably proceeds via the initial formation of a furfuryl carbocation. The key reagent (**4-4**) may be viewed formally as the bisthiomethyl acetal of nitro-acetic acid. Reaction of (**4-3**) with (**4-4**) leads to the displacement of one of the thio-methyl groups by the terminal amine on the side chain to give (**4-5**), probably by an addition-elimination sequence. Displacement of the remaining thiomethyl group by methylamine leads to the formation of the nitrovinyl function, a group that is bioiso-steric with a cyanoguanidine. There is thus obtained **ranitidine** (**4-6**).
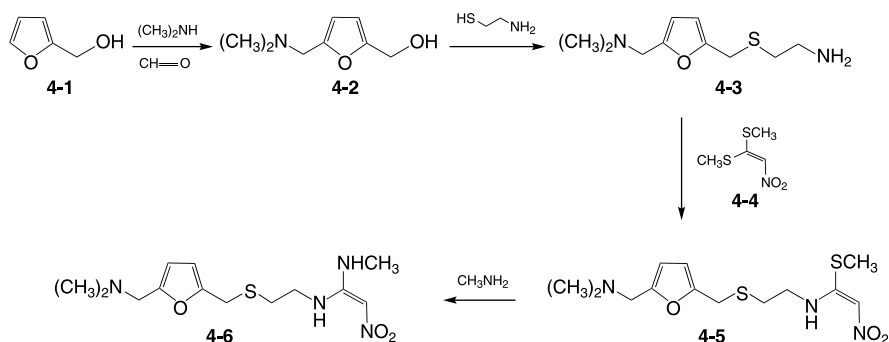
8.2.2. Pyrrole and Its Derivatives

8.2.2.1. NSAIDS and a "Statin". Benzene rings provide the aromatic nucleus for the majority of the NSAIDs. A propionic acid attached at its 2 position provides the side chain for most of these compounds, as noted in Chapter 2. Inhibition of the cyclooxygenase enzyme and consequently NSAID activity is retained when the role of an aromatic ring is filled by a pyrrole. The side chain for all but one of those compounds, it should be noted, consists of an otherwise unsubstituted acetic acid.

The starting material for the simplest of these compounds, **tolmetin (5-6)**, consists of the Mannich product (**5-1**) from a reaction of pyrrole itself with dimethylamine and formalin. Alkylation of that compound with methyl iodide gives the quaternary salt (**5-2**). Displacement of the now highly reactive benzyl-like salt with cyanide ion leads to the formation of the corresponding acetonitrile (**5-3**) with loss of the excellent leaving group, trimethylamine. Friedel–Crafts acylation of this last intermediate with the acid chloride (**5-4**) from *para*-toluic acid leads to the ketone (**5-5**). Hydrolysis of the nitrile group with an aqueous base affords the corresponding carboxylic acid and thus **tolmetin (5-6)** [5].
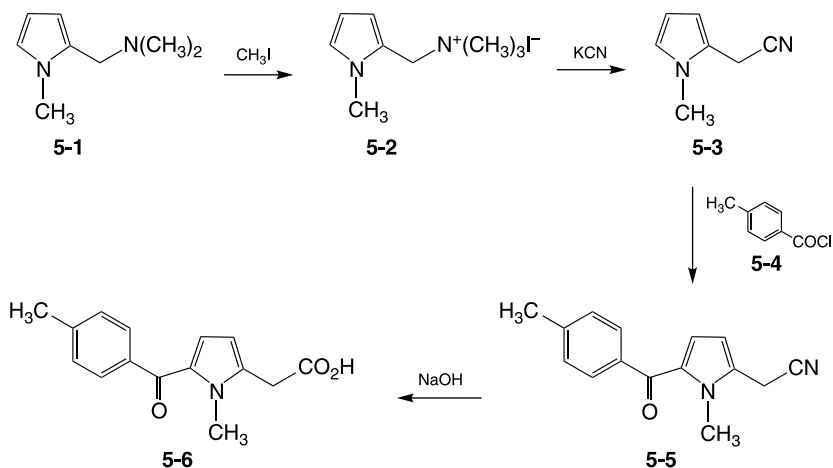
The preparation of the NSAID **clopirac** starts with the construction of the *N*-phenylpyrrole moiety. Thus reaction of *para*-chloroaniline (**6-1**) with the 2,5-dimethoxy furan (**6-2**), a latent form of hexane-2,5-dione, leads to the desired 2,5-dimethylarylpyrrole (**6-3**). Mannich reaction on that intermediate adds the first carbon of the side chain at only one of the two identical free positions on the pyrrole ring to afford (**6-4**). This is then converted to the nitrile (**6-5**) by the same sequence as above; hydrolysis to the corresponding acid then affords **clopirac (6-6)** [6].
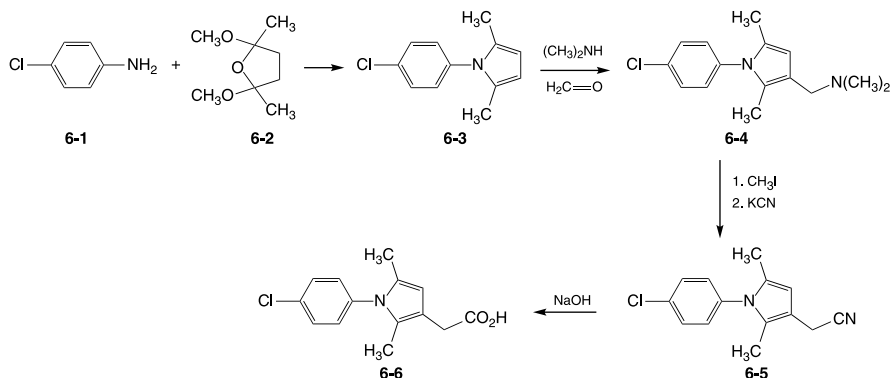
A modification of the classical Hantzsch synthesis provides a pyrrole ring that bears a prebuilt acetic acid chain. The reaction in this case involves the treatment of a mixture of ethyl acetonedicarboxylate, shown as its enolate (**7-1**), and chloroacetone with aqueous methylamine to give pyrrole (**7-4**) as the first observable product. The reaction can be rationalized by assuming the exchange of methylamine and hydroxyl to form enamine (**7-2**) as the first step; alkylation with chloroacetone will then give ketoester (**7-3**). Internal aldol condensation will then lead to the observed product (**7-4**). This is then saponified to a dicarboxylic acid; heating of that product leads to a loss of the ring carboxyl group. The remaining carboxyl group is then re-esterified (**7-5**) for protection in the next step. Friedel–Crafts acylation with the acid chloride from *para*-chlorobenzoic acid (**7-6**) occurs at the more reactive 2 position of the pyrrole ring. Saponification then gives the free acid, **zompirac** (**7-7**) [7].
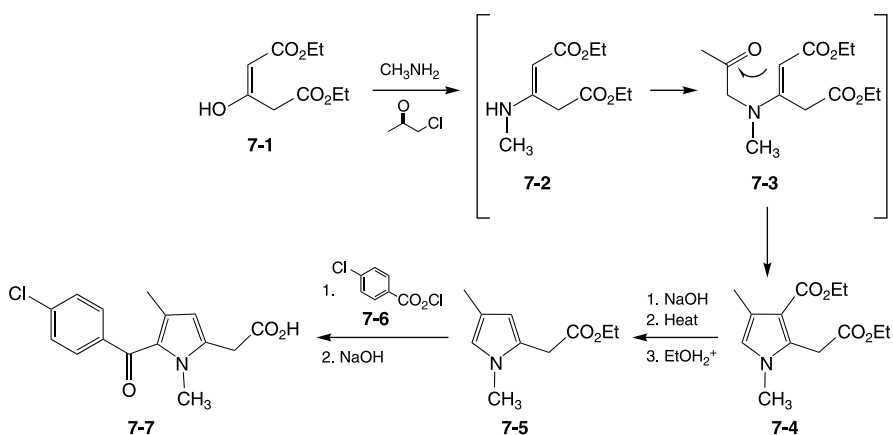
The carboxylic acid in the most active of these pyrrole NSAIDS, **ketorolac** (**8-8**), is actually disposed on an alicyclic ring fused onto the pyrrole; the connectivity of the carbon bearing acid is in fact closer to the better-known arylpropionic acid NSAIDS. The starting material (**8-1**) for the preparation of this agent is obtained by electrophilic substitution on the pyrrole proper by the sulfonium chloride obtained from the reaction of dimethyl sulfide with *N*-chlorosuccinimide. That intermediate loses a methyl group on heating, probably as chloromethane, to give the mercapto ether (**8-2**). The presence of the free pyrrole proton precludes normal Friedel–Crafts acylation. The bnzoyl group is added instead by a variation of the Villsmeier reaction in that (**8-2**) is treated with *N,N*-dimethylbenzamide and phosphorus oxychloride to give (**8-3**) on workup. Reaction of this intermediate with the spirocyclopropyl substituted Meldrum's acid derivative (**8-4**) in the presence of a base leads to an attack on the three-membered anion from pyrrolidine nitrogen to give the ring-opened intermediate (**8-5**). The sulfur is then oxidized to the sulfoxide by means of peracid to increase its propensity to act as a leaving group; methanolysis opens the dioxolane ring and leads to the key diester (**8-6**). Treatment with a strong base initially forms a carbanion at the

carbon bearing the two carboxylates; internal attack on the pyrrole ring leads to the displacement of the sulfoxide group, possibly by an addition-elimination sequence, and the formation of the fused ring to give (**8-7**). The sequence toward **ketorolac** (**8-8**) is completed by saponification of the ester groups and monodecarboxylation of the resulting di-acid [8].
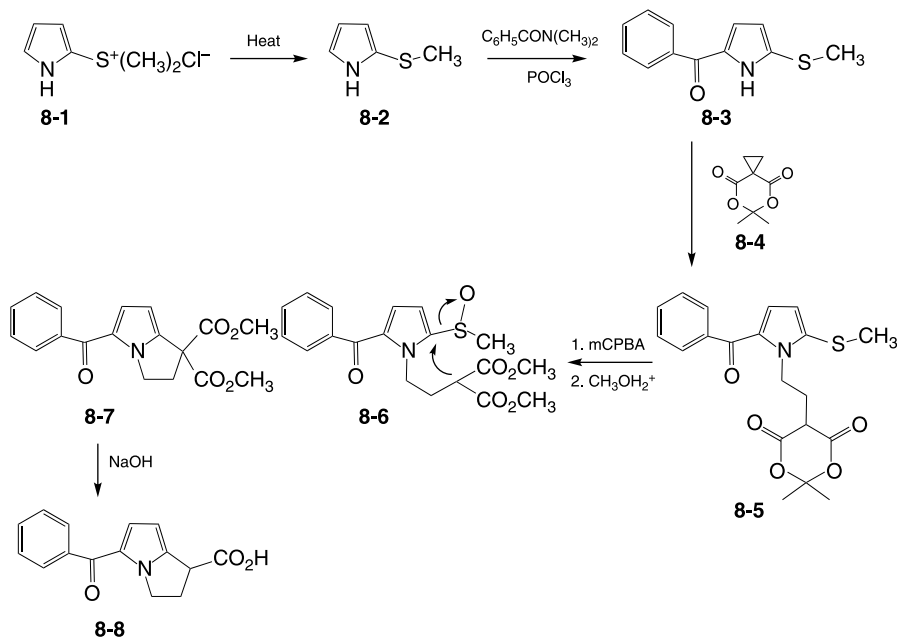
A significant portion of circulating cholesterol comprises compound synthesized *de novo* from acetate. Restricting the dietary intake of cholesterol or inhibiting its intake from ingested food will, as a consequence, have only a modest effect on serum cholesterol levels. A program aimed specifically at screening natural products that inhibit cholesterol synthesis led to the discovery of a fungal product, mevastatin, that interfered with an early stage in the biosynthesis. A key reaction in the synthesis of cholesterol comprises the reduction of hydroxyglutarate to mevalonic acid. Mevastatin, it was found, inhibits the enzyme hydroxymethylglutaryl CoA reductase best known by the acronym HMG-CoA reductase. The efficacy of the first-developed mevastatin related compounds in controlling serum cholesterol levels led to the development of a host of other compounds in what came to be called "statins." Very wide structural tolerance exists as to the nature of the lipophylic group R (**9-1**). All statins, however, share the chiral side depicted in (**9-1**) that mimics mevalonic acid [9]. One synthesis of the side chain found in the pyrrole based satin **atorvastatin** (**10-5**) starts by Claisen condensation of the chiral hydroxyl ester (**9-2**) with *tert*-butyl acetate to give the chain-extended keto-acid (**9-3**). Reduction of the carbonyl by means of sodium borohydride in the presence of methyl diethyl borate affords the 1,3-diol (**9-4**) as virtually a single diastereomer. The borate in all likelihood complexes with the hydroxyl in the starting material so as to transfer chirality to the newly

forming carbinol. The hydroxyl groups are then tied up as their acetonide (**9-5**) by reaction with acetone. The nitrile is then reduced to a primary amine (**9-6**) by hydrogenation over Raney nickel in the presence of ammonia [10].
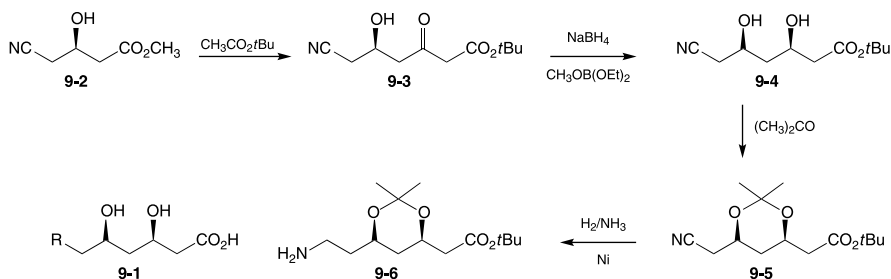
Synthesis of the group represented by R in (**9-1**) starts by piperidine catalyzed Knoevnagel condensation of the β-ketoamide (**10-1**) with benzaldehyde to afford (**10-2**) as a mixture of geometric isomers. Reaction of that acrylate with 4-fluoro-benzaldehyde in the presence of *N*-butyl-4-hydroxyethylthiazolium chloride (HMTC) in effect comprises an umpolung reaction where the anion from the removal of the proton on the aldehyde function undergoes conjugate addition to the enone in (**10-2**), leading to the addition product (**10-3**). Condensation of the 1,3 dicarbonyl array in this intermediate with the primary amine on the side chain fragment (**9-6**)
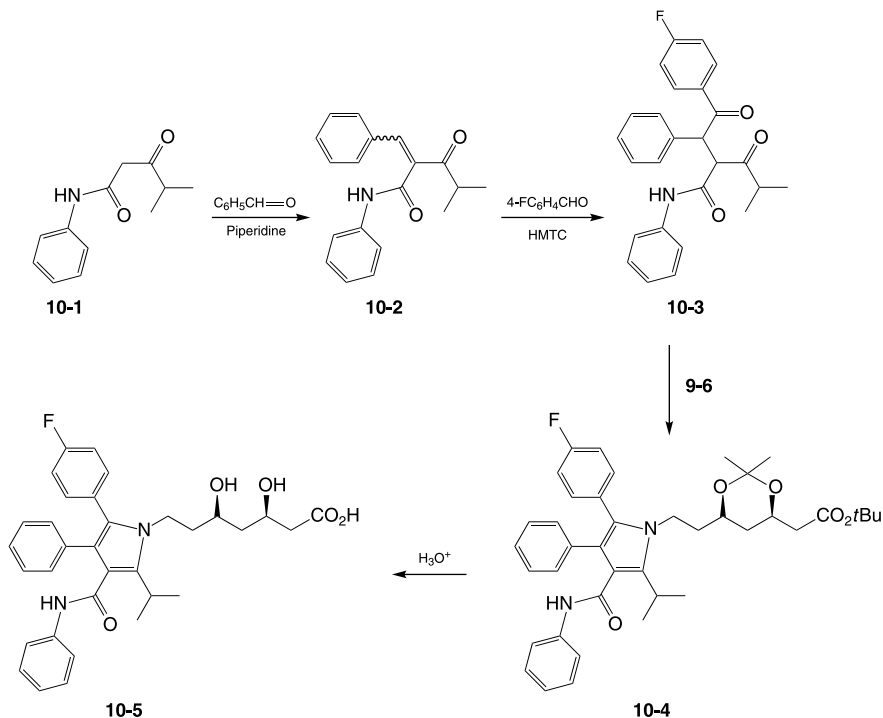
leads to the formation of a pyrrole ring while at the same time incorporating the side chain (**10-4**). Acid hydrolysis then serves to remove the acetonide protecting group as well as the *tert*-butyl ester. There is thus obtained the acid diol (**10-5**) **atrovastatin** [11].

8.2.2.2. *ACE Inhibitors.*

The renin-angiotensin system plays a pivotal role in the maintenance of the circulatory system, exerting control over blood volume and pressure as well as levels of tissue sodium and potassium. Angiotensin II, the controlling octapeptide, as noted in the discussion of protease inhibitors in Chapter 1, is actually the product of a degradative scheme that starts from the large peptide angiotensinogen. Reaction of the decapeptide product, angiotensin I, from renin catalyzed cleavage of the latter with angiotensin-converting enzyme (ACE) leads to the vasoconstrictor angiotensin II. The development of ACE inhibitors as antihypertensive drugs was spurred at least partly by the observation of the hypotensive effect and ACE inhibiting activity of a nonapeptide from the venom from the snake *Bothropos jararaca*. This compound and its successors all inhibit ACE by acting as false substrates at a cleavage site on the enzyme. A synthesis program aimed at finding an orally effective nonpeptide counterpart culminated in the identification of **captopril** (**11-4**) [12]. The mechanism of action is reflected in the fact that both this compound and its successors retain some peptide-like features, as is the fact that the drugs are also all single enantiomers.

In one synthesis of this drug, L-proline (**11-2**) is acylated with the acid chloride (**11-1**) obtained from the addition of hydrogen chloride to the double bond in methacrylic acid followed by reaction with thionyl chloride to give amide (**11-3**) as a mixture of diastereomers. The pure 2*S* isomer is then isolated from the mixture by fractionation as the dicyclohexylamine salt. Treatment of that compound with ammonium hydrosulfide leads to the displacement of chlorine by a thiol group and the formation of **captopril** (**11-4**) [13].
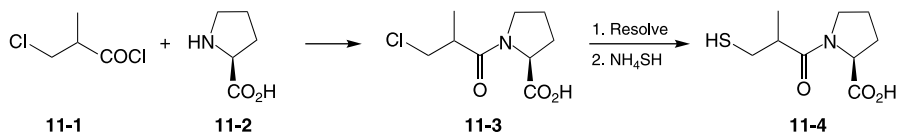
The effectiveness of ACE inhibitors as antihypertensive agents combined with the low incidence of side effects led to the intensive investigation of the SAR of this class of drugs. Replacement of the methylthiol fragment by an alkylated amino group formally changes that fragment to an alanine derivative; the core of the structure thus becomes a dipeptide. Compounds in this series have proven to be very active ACE inhibitors when the alkylating function is provided with an additional carboxyl group. Reductive alkylation of the dipeptide alanylproline (**12-2**), prepared by standard coupling methods, with ketoester (**12-1**) and hydrogen leads directly to

the secondary amine (**12-3**) as a mixture of diastereomers in which the desired product predominates. This is then isolated by a crystallization as its maleate salt to give the antihypertensive drug **enalapril** (**12-3**) [14]. It has been established that the active agent is in fact the dicarboxylic acid **enalaprilat** that results from *in vivo* saponification. This last product is, however, not active by the oral route probably as a result of its highly polar nature.
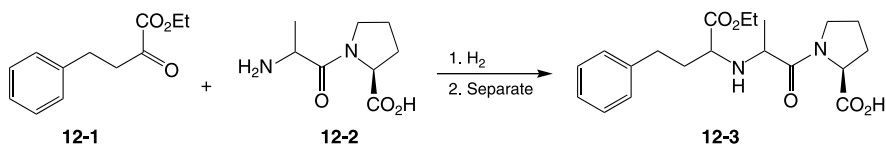
The replacement of alanine residue by a lysine moiety leads to **lisinopril** (**13-2**) administered in this case as a free dicarboxylic acid; this compound that is quite active orally in spite of its polarity. The synthesis is quite analogous to that above, involving reductive alkylation of *tert*-butoxycarbonyl protected lysilproline (**13-1**) with ketoester (**12-1**). Separation of the desired diastereomer followed by the removal of the BOC group with trifluoroacetic acid and then saponification gives **lisinopril** (**13-2**) [14].
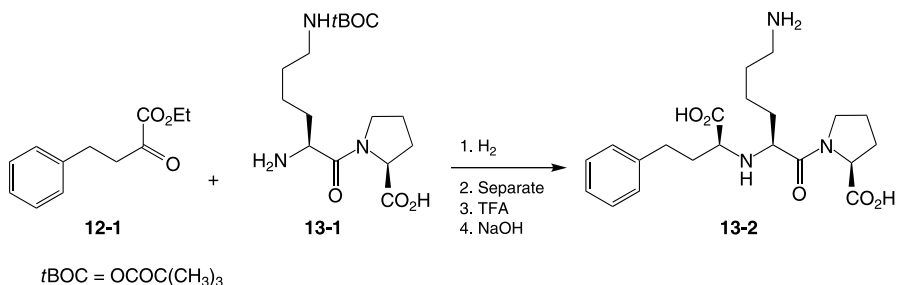
Oxidized phosphorus included as part of the alanyl residue can also serve as the second acidic group. The required side chain (**14-2**) is prepared by the addition of the free radical from treatment of the sodium salt of phosphinic acid with azobisisobutyronitrile (AIBN) to 4-phenylbut-1-ene (**14-1**). Dicyclohehylcarbodiimide mediated amide formation between the carbobenzyloxy (CBZ) derivative of the lysine derivative (**14-3**), in which a hydroxyl group replaces the amine, and the benzyl ester of L-proline (**14-4**) affords the amide (**14-5**). Reaction of the hydroxyl group in (**14-5**) with the phosphonic acid (**14-2**) in the presence of DCC leads to the formation of an ether bond to give the intermediate (**14-6**). Oxidation of the phosphine P—H bond with peracid leads to a phosphinic acid. Catalytic reduction of the product leads to cleavage of both the benzyl based protecting groups; there is thus obtained **ceronapril** (**14-7**) [15].
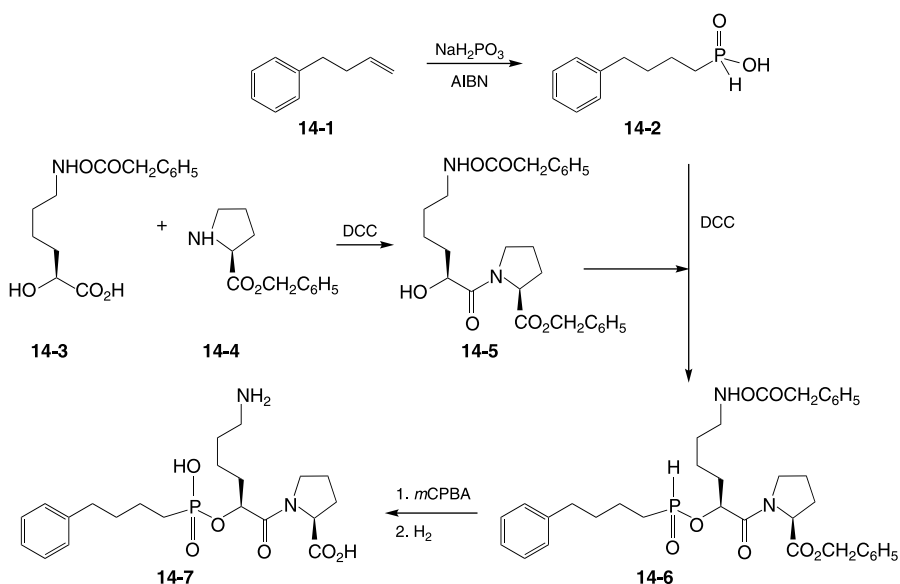
Considerable latitude also seems to exit for the structural modification of the proline moiety. This ring may form part of an indole, an indoline, or even a tetrahydro-isoquinoline. A less profound change involves the fusion of a spirothioacetal onto the pyrrolidine ring. Thus, reaction of the CBZ derivative of 3-ketoproline methyl ester (**15-1**) with ethane-1,2-thiol affords the corresponding thiocacetal (**15-2**). The CBZ group is then removed by hydrogenolysis over palladium and the resulting free amine coupled with an appropriately protected alanine derivative to afford the dipeptide-like intermediate (**15-3**). This is then subjected to reductive alkylation with the same ketoester as that used above. Separation of the desired isomer gives the ACE inhibitor **spiralpril** (**15-4**) [16].
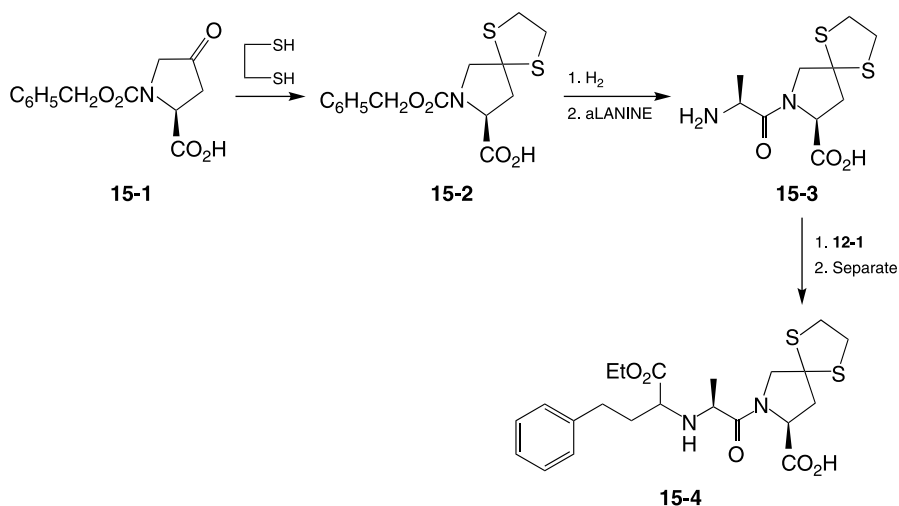
ACE inhibiting activity is retained when the pyrrolidine ring of the proline moiety is imbedded in fused bicyclic system; this modification leads to several quite potent antihypertensive drugs.

Construction of the hetero-bicyclic fragment starts with alkylation of the enamine (**16-1**) from cyclopentanone with the chloro derivative (**16-2**) obtained in several steps from *N*-acetyl serine to give amidoketone (**16-3**) as the product. Treatment of the latter with aqueous acid can be viewed as involving initial hydrolysis of the acetamide; imine formation between the thus freed primary amine and the adjacent carbonyl group will lead to the formation of the dihydropyrrolidine ring; hydrolysis of the ester group in the acid medium leads to the formation of iminoester (**16-4**) as a mixture of stereoisomers. The acid is then converted to its benzyl ester and this resolved; hydrogenolysis then affords the desired isomer (**16-5**). The first step in the preparation of the alanine based side chain involves conjugate addition of the benzyl ester of alanine (**16-7**) to the unsaturated ketoester (**16-6**), with the addition occurring at the terminus of the double bond conjugated with the ketone to give the intermediate (**16-8**) as a mixture of diastereomers; that intermediate with stereo-chemistry corresponding to (**16-8**) is then isolated. Exhaustive catalytic hydrogen-ation over palladium removes the benzyl protecting group and at the same time reduces the ketone to a methylene group via hydrogenolysis of the initially formed carbinol; there is thus obtained the completed side chain (**16-9**). DCC mediated coupling between this side chain and the amino group in (**16-6**) results in the formation of the ACE inhibitor **ramipril** (**16-10**) [17,18].
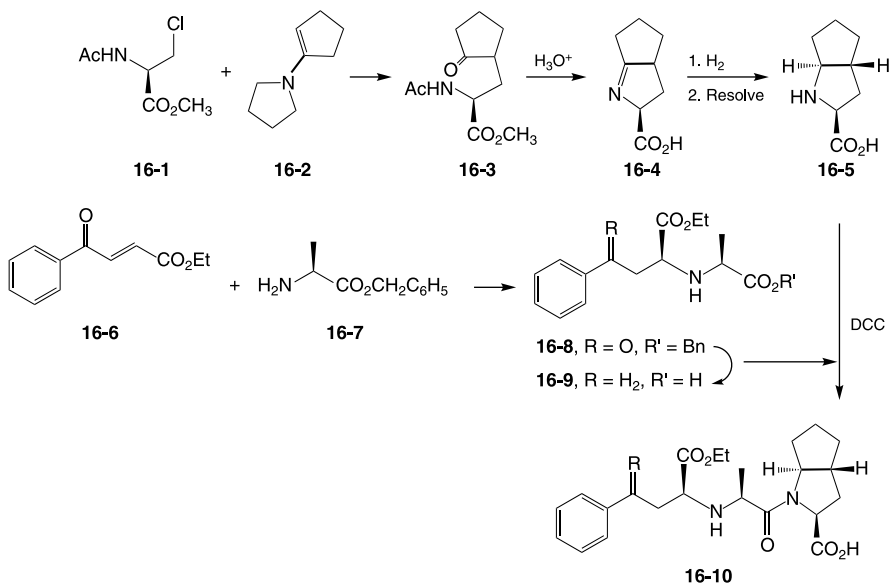
The nucleus of the ACE inhibitor **perindopril** (**17-6**) consists, as the name suggests, of a perhydroindole; the compound also differs from the foregoing examples by omitting the benzene ring on the side chain terminus. The side chain

(**17-3**) for this compound is obtained in a single step by sodium cyanoborohydride-mediated reductive amination of pyruvic acid (**17-2**) with *S*-norvaline (**17-1**). The reaction can be visualized as involving first the formation of an imine between the primary amine and the ketone; the proximity of this newly formed bond to the chiral carbon on the amino acid results in stereoselective reduction and the consequent formation of (**17-3**) as a single diastereomer. Exhaustive hydrogenation of the ester (**17-4**) of chiral indoline 2-acetic acid leads to the totally reduced derivative with the *cis* ring fusion. The compound is then saponified and the acid protected as its *tert*-butyl ester (**17-5**) by treatment with isobutylene. Coupling of this last product with the side chain (**17-3**) followed by removal of the protecting group affords **perindopril** (**17-6**) [19].
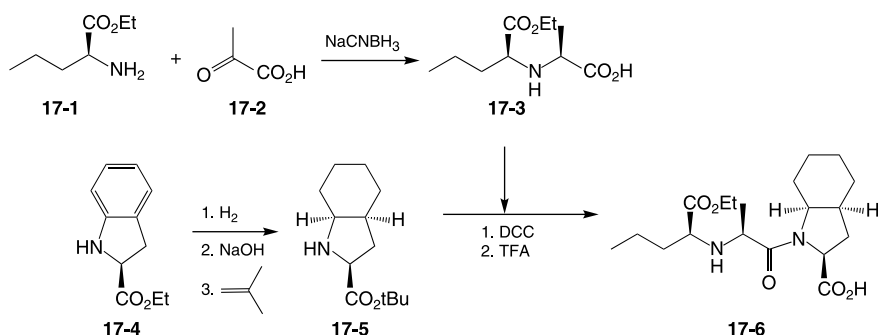
A counterpart of (**17-6**) in which the proline is incorporated in an indoline has a markedly altered peptidomimetic side chain that brings to mind the statine-based protease inhibitors discussed in greater detail in Chapter 1. Chiral indoline carboxylic acid (**18-1**) is obtained by first resolving the corresponding acetamide and then saponifying the resulting product. The key half-ester (**18-2**) can be obtained by careful ethanolysis of *meso* 2,4-dimethylglutaric anhydride, a compound in which both carboxyl groups are sterically identical. Coupling the two synthons by means of DCC gives **pentopril** (**18-3**) [20].
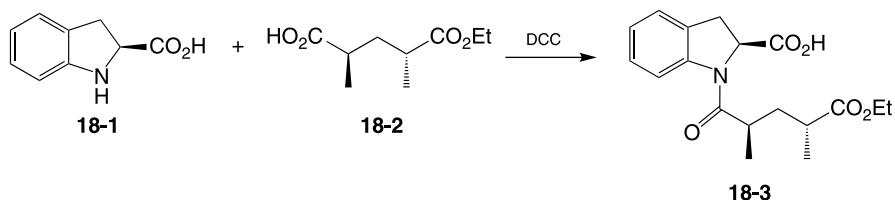
Quite analogous methodology is used to prepare a ring enlarged version of the foregoing; the resulting tetrahydroisoquinoline derivative, **quinapril** (**19-3**), does, however, retain a peptide-like side chain. The heterocyclic nucleus for this ACE inhibitor is obtained by Pictet–Spengler condensation of *S*-phenylalanine (**19-1**) with formaldehyde in the presence of sulfuric acid. The reaction, which probably proceeds via an intermediate imine, affords the heterocycle as predominantly a single

enantiomer. The carboxylic acid is then converted to it *tert*-butyl ester by reaction with isobutylene to give aminoester (**19-2**). The final product (**19-3**) is obtained by acylation of this with the acid (**16-9**), whose preparation is described above, followed by acid catalyzed removal of the *tert*-butyl ester protecting group [21].
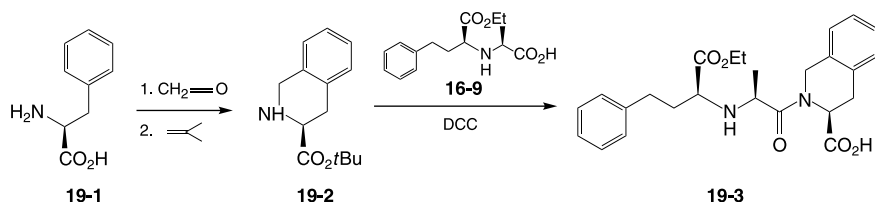
8.2.2.3. Miscellaneous Compounds.
A saturated spirocyclic pyrrolidine serves as the nucleus for a diamine that has been described as a hypolipemic agent. Treatment of the carbanion of the substituted cylcohexane carboxylic ester (**20-1**) with methyl bromoacetate leads to the alkylation and formation of the diester (**20-2**). Saponification of the ester groups followed by reaction with acetic anhydride leads to ring closure of the succinic anhydride (**20-3**). Condensation with ammonia leads to the succinimide (**20-4**). The side chain is then added by alkylation of the anion on nitrogen with 1-bromo-4-dimethylaminobutane (**20-5**). Reaction of this last intermediate with lithium aluminum hydride leads to the reduction of the carbonyl groups to methylene. This affords the pyrrolidine (**20-6**) **atiprimod** [22].
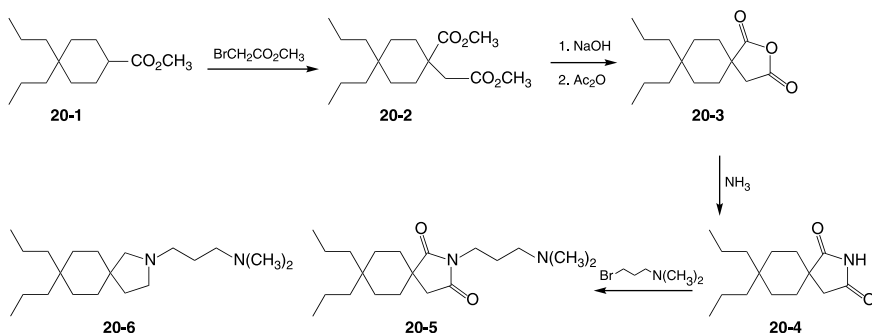
The hormone-like peptide incretin stimulates the release of insulin by a feedback process that involves cleaving the molecule to an inactive form. The protease enzyme dipeptidal peptidase (DPP) in turn cleaves incretin, in effect inactivating this enzyme. Inhibition of DPP consequently extends the action of incretin. This inhibition thus prevents the increased levels of blood glucose that mark diabetes. The protease inhibitor **vidagliptin**, which is modeled in part on the terminal sequence in DPP, has been found to sustain levels of insulin in Type II diabetics. The inhibition is apparently reversible in spite of the presence in the structure of the relatively reactive α-aminonitrile function. Construction of one intermediate in the convergent synthesis comprises the reaction of amino adamantamine (**21-1**) with a mixture of nitric and

sulfuric acid. This affords the product (**21-2**) from the nitration of one of the remaining unsubstituted ternary positions. Treatment of this product with a strong base leads to solvolysis of the nitro group to give aminoalcohol (**21-3**). Preparation of the other moiety involves first the acylation of the pyrrolidine (**21-4**) with chloro-acetyl chloride to give amide (**21-5**). Reaction of that intermediate with trifluoracetic anhydride converts the amide at the 2 position to the correspounding nitrile. Alkylation of the adamantamine (**21-3**) with (**21-6**) proceeds on nitrogen to afford **vidalgliptin** (**21-7**) [23].
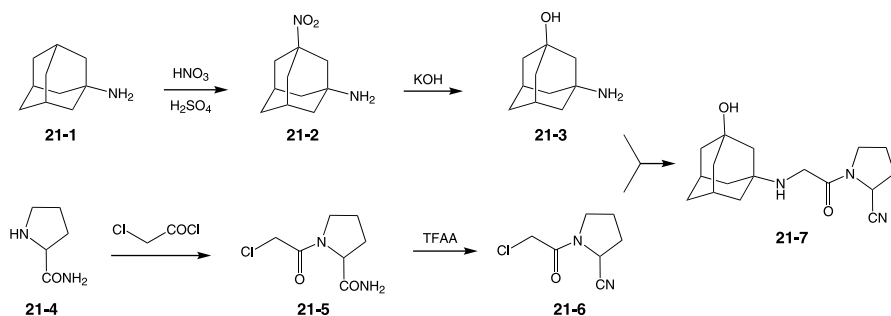
A substituted pyrrolidine that acts as a DPP inhibitor comprises another example in which this ring serves as a surrogate for proline. This compound is being investigated as an anticancer drug as a result of the finding that it inhibits the growth of tumors in various animal models. The structure of this compound is notable for the rare occurrence of boron in the structure, in this case in the form of a covalently bound boronic acid. The final compound, **talabostat**, comprises a single enantiomer. This is accomplished in the case at hand by a stereoselective synthesis rather than by resolution of the final compound or an intermediate. The first step in the synthesis comprises protecting the amine in pyrrolidine (**22-1**) by conversion to its *tert*-butoxy-carbonyl derivative (**22-2**, BOC) with *tert*-butoxycarbonyl anhydride. Reaction of the product with butyl lithium generates an anion on carbon next to nitrogen. Treatment of this with triethyl borate displaces one of the ethoxy groups in the reagent to form a carbon—boron bond. The product comprises a $1:1$ mixture of enantiomers. Hydrolysis of this intermediate then affords the corresponding boronic acid (**22-3**). A key step involves the formation of the acetal-like compound of (**22-3**) with naturally occurring (+) pinanediol (**22-4**). The initial product comprises two diastereomers due to the fact that the starting boronic acid (**22-3**) itself consists of two enantiomers. The pair of diastereomers of (**22-5**) is then separated by recrystallization. In the next step, the BOC group of the desired isomer is removed (**22-6**). The free amine is next coupled with the BOC derivative from valine (**22-8**) to give the amide (**22-9**). Treatment of this last intermediate with acid removes the BOC protecting group (**22-10**). The pinane diol group is then removed by exchange with excess phenyl boronic acid. The final compound is converted to a salt to avoid the formation of a stable zwitterion between the amine and the boronic acid function. There is thus obtained **talabostat** (**22-11**) [24].
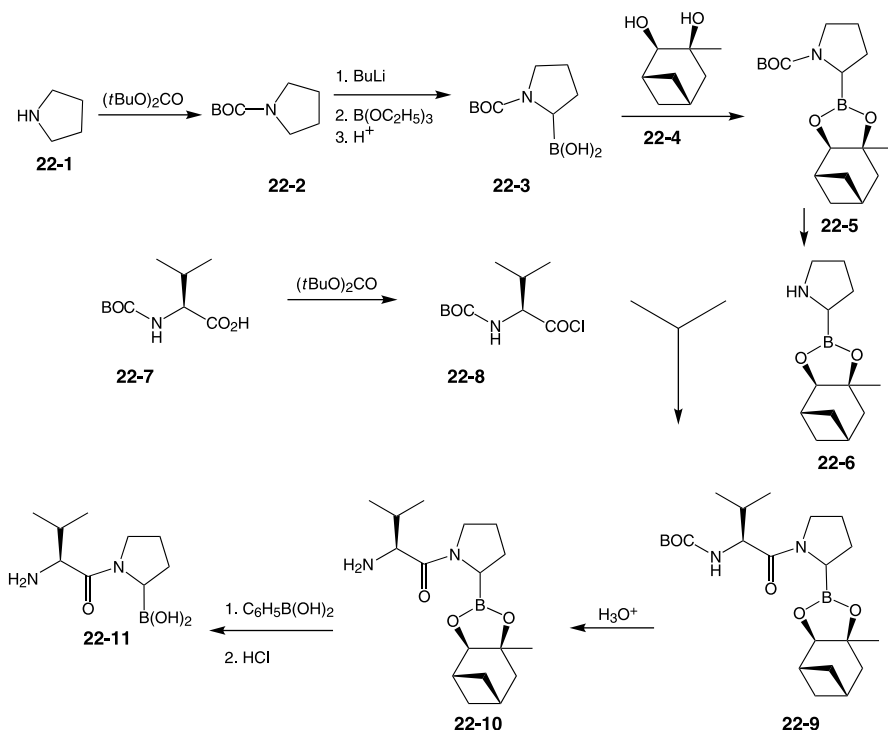
Endothelins rank among the most potent known vasoconstricting agents; they have been implicated in a number of diseases, including cerebral vasospasm and pulmonary hypertension. The stereoselective synthesis of an endothelin antagonist begins with the establishment of the chiral locus that will dictate the remaining asymmetric centers. Oxazolidone (**23-2**) derived from valine serves as the chiral auxiliary for that step. Condensation of the mixed anhydride (**23-1**) from piperonalacetic acid with the anion from auxiliary (**23-2**) gives the corresponding amide (**23-3**). Treatment of that intermediate with a strong base followed by *tert*-butyl bromoacetate leads to the alkylation product (**23-4**) as virtually a single isomer. The auxiliary heterocycle is then removed by means of lithium hydroperoxide to afford the half-ester (**23-6**). Reaction of that with diborane selectively reduces the free acid to give the ester alcohol (**23-7**). The hydroxyl group is then activated by conversion to its tosylate (**23-8**). Treatment of that intermediate with anisyl hydroxylamine (**23-9**) in the presence of cesium carbonate affords the *O*-alkylated derivative (**23-10**). The ester grouping is then exchanged with methyl orthoformate to afford the methyl ester (**23-11**). Reaction of this last intermediate with trimethylsilyl triflate and butylamine in the presence of 1,2-dichloroethane presumably forms an anion-like species on the carbon adjacent to the ester. This then adds internally to the oxime carbon atom to yield a 1,2-oxazine. This product (**23-12**) predominates over the diastereomer in a 9 : 1 ratio.
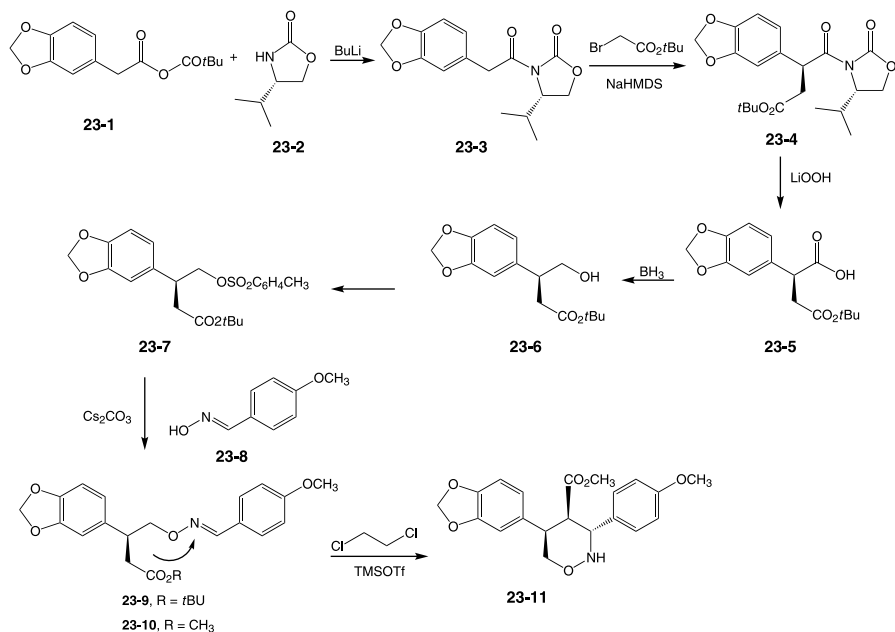
Catalytic hydrogenation of (**23-12**) over palladium on charcoal results in the scission of the weak N—O bond and the formation of amino alcohol (**24-1**). This is converted to a pyrrolidine by an internal alkylation reaction. Thus, reaction of the intermediate with carbon tetrabromide and triphenyl phosphine presumably converts the alcohol to a bromide; internal displacement by the primary amine forms the five-membered ring (**24-2**). Alkylation of that amine with the complex bromo amide (**24-3**) then affords the endothelin antagonist **atrasentan** (**24-4**) [25].
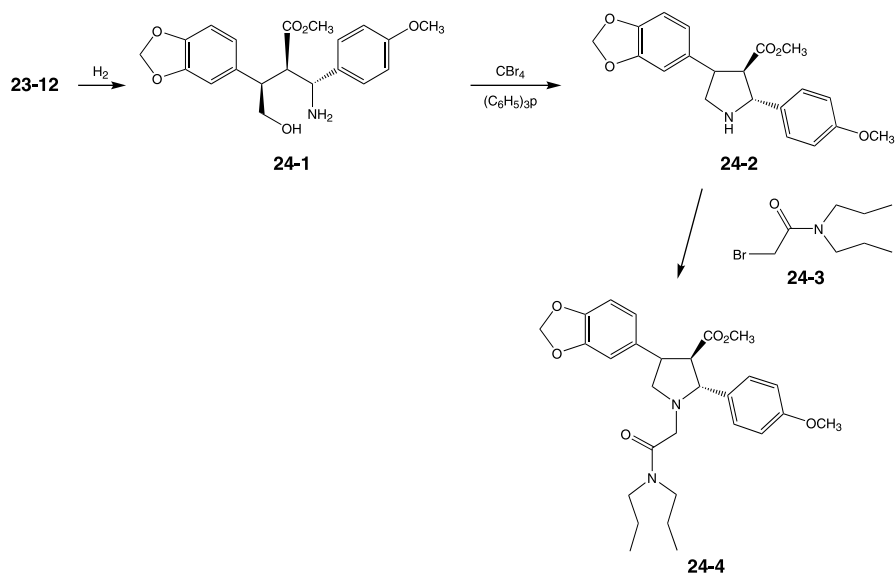
Research on anticholinergic compounds has experienced something of a resurgence as a result of their utility in treating conditions such as urinary incontinence. The structures of these compounds are quite varied, as shown by **darfenacin (25-11)**, which differs considerably from other compounds in this class. The synthesis of this compound (**25-11**) is also designed to produce a single enantiomer. Heat induced decarboxylation of proline (**25-1**) affords the key intermediate (**25-2**) as a pure enantiomer. The amino group is then converted to its tosylate (**25-3**) with toluenesulfonyl chloride; the hydroxyl group interestingly does not react under those conditions. Converting that group to its derivative is accomplished by Mitsonobu reaction with methyl tosylate to give the doubly derivatized intermediate (**25-4**). Condensation of that with the anion from diphenyl acetonitrile (**25-5**), produced by reaction with sodium hydride, gives the alkylation product (**25-6**). Treatment of this intermediate with hydrogen bromide removes the protecting group on nitrogen. The nitrile is then converted to the corresponding amide with sulfuric acid (**25-7**). In a converging scheme, acylation of benzofuran (**25-8**) with chloroacetyl chloride and aluminum chloride yields the chloroketone (**25-9**). Reaction of that with pyrrolidine (**25-7**) leads to the alkylation product (**25-10**). Catalytic hydrogenation over palladium reduces the aryl carbonyl group to a methylene probably via the initially formed labile benzyl alcohol. There is thus obtained the anticholinergic agent **darifenacin (25-11)** [26].
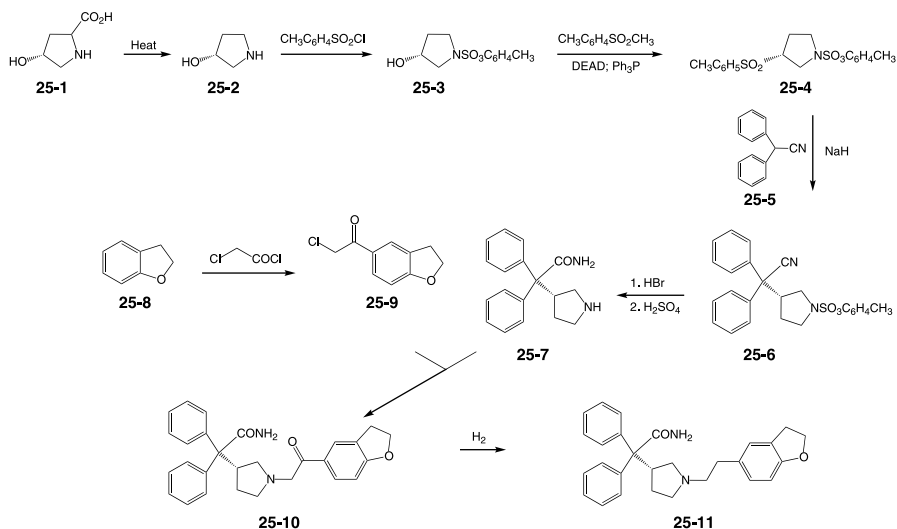
An unusual rearrangement provides the key to the preparation of a highly substituted pyrrolidone, **doxapram (26-7)**, that is used as a respiratory stimulant. The synthesis starts with the displacement of chlorine on pyrrolidine (**26-1**) by the carbanion from diphenylacetonitrile (**26-2**) to give (**26-3**) as the product. The quite hindered nitrile is then hydrolyzed to the corresponding carboxylic acid (**26-4**) by basic hydrolysis. The reaction of acid with thionyl chloride presumably proceeds initially to form the corresponding acid chloride. The close proximity of that group to basic

nitrogen, which is not readily apparent from planar drawings, leads to the internal reaction of those functions to form the reactive bicyclic quaternary acylation product (**26-5**). The chloride counterion liberated in reaction then displaces one of the more electrophilic branches of the caged structure. This leads to a ring opening to a pyrrolidone (**26-6**) with the simultaneous formation of a halogenated side chain. The displacement of chlorine by nitrogen on morpholine leads to the alkylation product, **doxapram (26-7)** [27].
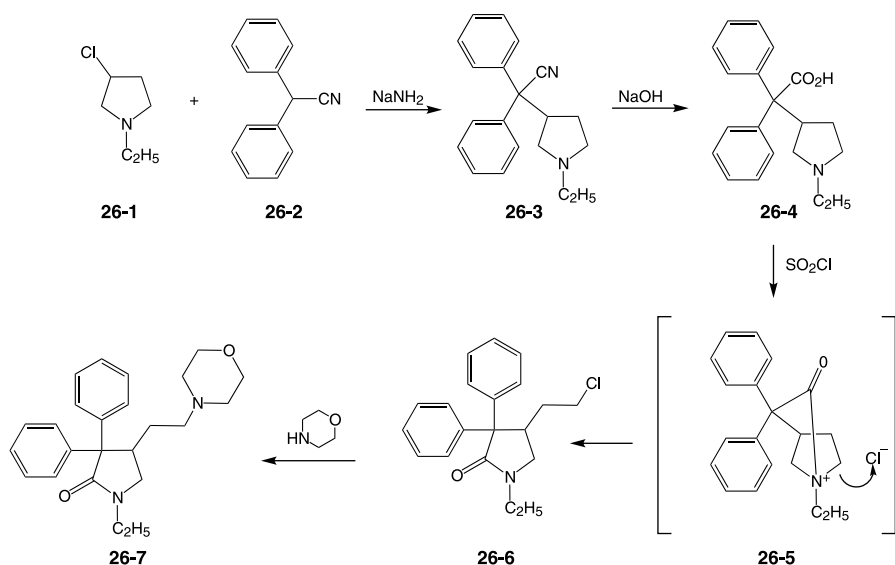
There exists ample evidence for the increase in potency that can be achieved by the addition of substituents on the ethylamine fragment at in the sulfonylurea antidiabetic series (see, for example, glyburide in Chapter 2). Reaction of pyrrolidinone (**27-1**) with the isocyanate from phenethylamine (**27-2**) leads to urea (**27-3**). The
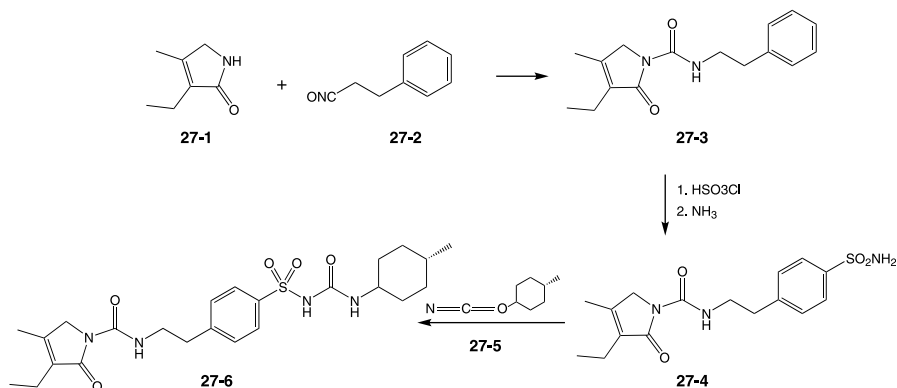
sulfonamide function is then added in the customary fashion by sequential reaction with chlorosulfonic acid followed by ammonia. Treatment of the resulting sulfonamide with the isocyanate from *trans*-4-methylcyclohexylaminde (**27-5**) puts in place the requisite sulfonylurea function. There is thus obtained the hypoglycemic agent **glimepiride** (**27-6**) [28].

Hydantoins, that is, imidazo-2,4-diones, as noted in the discussion of imidazole derivatives that follows, comprise one of the oldest and perhaps most effective class of anticonvulsant drugs for the treatment of epilepsy. Several somewhat simpler imides have also found some use for this indication, though these compounds are said to act mainly on petit mal seizures. The synthesis of a typical agent, **phensuximide** (**28-4**), starts with the conjugate addition of cyanide ion to the product (**28-1**) from Knoevnagel condensation of benzaldehyde with ethyl cyanoacetate. Acid hydrolysis of the adduct (**28-2**) proceeds initially to a tricarboxylic acid; decarboxylation of the thus-formed β-dicarboxylic acid leads to the observed product, succinic acid (**28-3**). Reaction of the acid with methylamine leads to the formation of the imide ring and thus (**28-4**) [29]. The same sequence starting from the Knoevnagel product (**28-5**) from acetophenone affords the anticonvulsant agent **methsuximide** (**28-8**) [29].
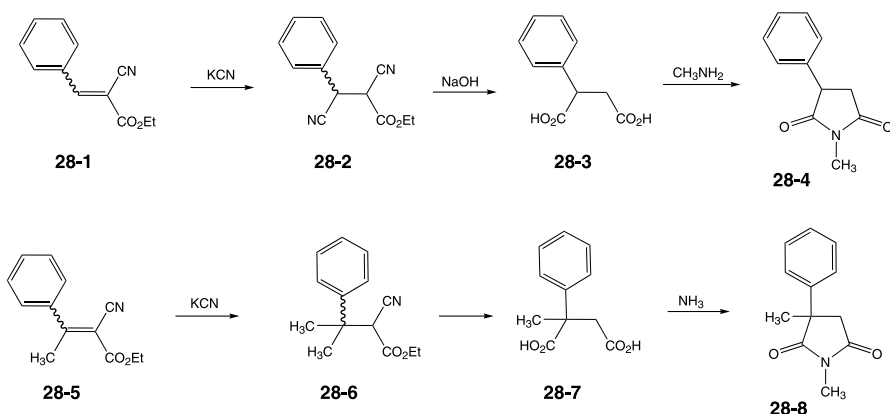
The first report of the preparation of the dialkyl succinimide (**29-3**) dates back to early in the twentieth century. It is consequently surprising to note that it was introduced as an anticonvulsant, under the name **ethosuximide**, well after its more recently synthesized congeners. The synthetic route starting from methyl ethyl ketone generally follows that above with the exception of the use of ammonia in the last step. The compound thus differs as well by possessing a somewhat acidic imide proton [30].
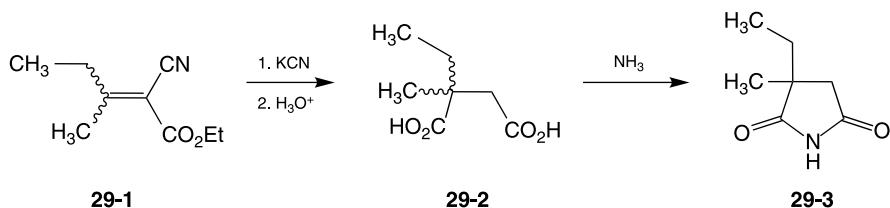
Leukotrienes, products from one branch of the arachidonic cascade, are closely associated with symptoms of allergy as well as asthma. The benzothiophene-based leukotriene antagonist, **zileuton**, one of the first agents in this class, is now on the market. A related compound, **atreluton**, which omits the fused benzene ring present in the prototype, shows improved potency and duration of action over its predecessor. Condensation of benzyl bromide (**30-1**) with the anion from thiophene and butyl lithium in the presence of the Heck catalyst (tetrakis triphenyl phosphine · paladium) gives the coupling product (**30-2**). Reaction with *N*-bromosucimide leads to the bromo thiophene (**30-3**). Condensation of that intermediate with the methyl-ethynyl carbinol in the presence of triphenyl phosphine, Heck catalyst, and cupric iodide leads to the coupling product (**30-4**). The requisite functionality is constructed by first replacing the hydroxyl next to the acetylene by nitrogen. Mitsonobu-like reaction with *O,N bis*-phenyloxycarbonyl hydroxylamine in the presence of triphenylphosphine and diethylazodicarboxylate (DEAD) affords (**30-5**). Reaction of that intermediate with ammonia leads to the displacement of both phenoxy groups. This leads to the formation of the free hydroxyl from the *O*-carbonate and a urea from the phenoxy ester, yielding the leukotrienes antagonist atreluton (**30-6**) [31].
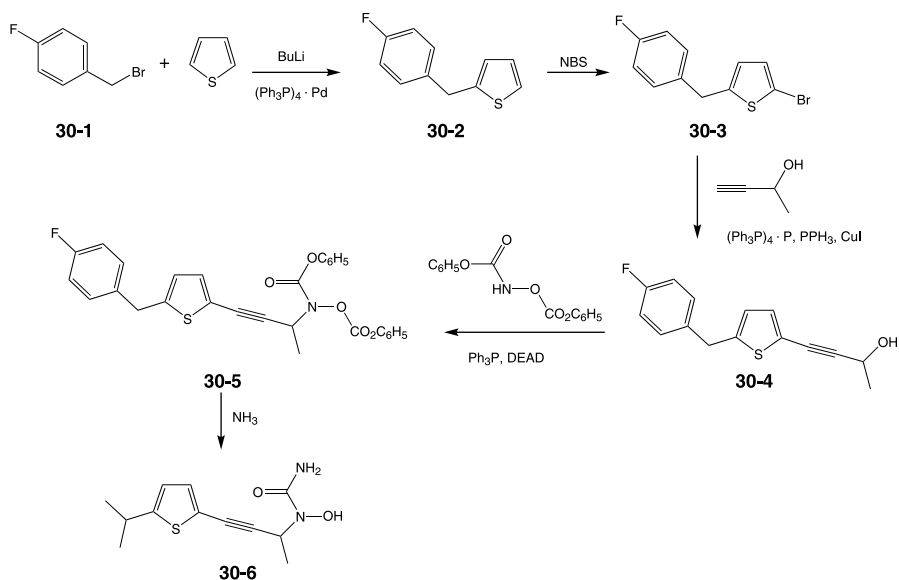
8.3. RINGS THAT CONTAIN TWO HETEROATOMS

8.3.1. Cyclooxygenase 2 (COX-2) Inhibitor NSAIDs

The discovery that a subtype cycloxygenase enzyme, COX-2, does not inhibit the formation of stomach-protecting prostaglandins paved the way for a series of NSAIDS whose structures depart markedly from the carboxylic acid-based drugs

such as the profens. The diversity of five-membered heterocycles that provide the nucleus for COX-2 inhibitors makes it convenient to discuss these as a group, admittedly doing violence to the organizing principle of this tome. The enormous success of the first agent on the market, **celecoxib**, led to detailed investigations of the SAR of this class in competing laboratories. Preparation of the lead compounds starts with Claisen condensation of the acetophenone (**31-1**) with ethyl trifluoracetate in the presence of sodium hydride to afford the β-diketone (**31-3**). Condensation of that with the phenylhydrazine (**31-4**) proceeds to form a pyrazole ring. The regiochemistry may be rationalized by assuming that the first step involves an initial reaction of the more basic terminal nitrogen with the more electrophyllic carbonyl adjacent to the trfluoromethyl group. Reaction of the remaining nitrogen then closes the ring to afford celecoxib (**31-5**) [32].
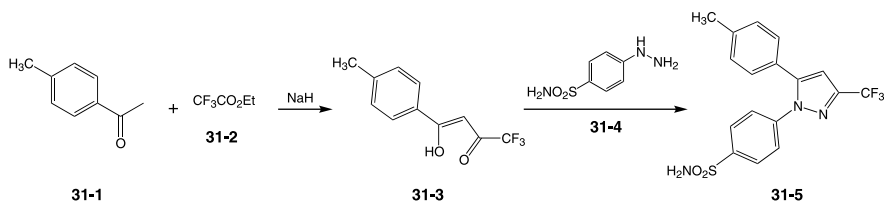
The minimum requirement for activity seemed to involve two aromatic rings on adjacent positions on a five-membered heterocyle. The very recent entry, **tilmacoxib**, shows that one of those benzene rings can be replaced by cyclohexane. Condensation of meta-fluorobenzyl bromide (**32-1**) with the acid chloride (**32-2**) from cyclohexane carboxylic acid in the presence of a Heck reagent affords the ketone (**32-3**) that incorporates the requisite two rings. Bromination proceeds on the benzylic position to afford (**32-4**). That reactive halogen is then displaced with acetate to give the key intermediate (**32-5**). Construction of the heterocyclic ring involves the reaction of this last intermediate with ammonium acetate. The reaction can be viewed for bookkeeping considerations as proceeding through an initial reaction of ammonium ion with the ketone to form an imine. This then cyclizes with the adjacent carbonyl on the acetate to afford (**32-6**). Treatment of this product with chlorosulfonic acid gives the sulfonyl chloride, which is immediately allowed to react with ammonia

to yield the corresponding sulfonamide. This then affords the COX-2 inhibitor tilmacoxib (**32-7**) [33].

The oxazole ring can also be replaced by an isoxazole. Reaction of deoxybenzoin (**33-1**) with hydroxylamine affords the oxime (**33-2**). Treatment of this intermediate with two equivalents of butyl lithium followed by acetic anhydride goes to the hydroxyl isoxazoline (**33-4**). The transform can be rationalized by assuming that this proceeds via the *O*-acylated intermediate (**33-3**). The anion from the benzylic position would then add to the acetyl carbonyl group to afford the observed product. Reaction of that compound with chlorosulfonic acid results in the sulfonation of the aromatic ring nearest the nitrogen. The first step probably comprises the dehydration of tertiary alcohol in (**33-4**) under strongly acidic conditions to give (**33-5**). The subsequent addition of ammonia converts the chlorosulfonic acid to the corresponding sulfonamide and thus **valdecoxib** (**33-6**) [34]. Reaction of this compound with acetic anhydride leads to the acylation of the amide nitrogen. This increases the acidity of that already acidic function. Treatment with a base affords the water-soluble salt **parecoxib** [35] (**33-7**) suitable for use in injectable formulations.

The imidazole ring, too, is represented among COX-2 NSAIDs. Reaction of sulfonyl chloride (**34-1**), available from the chlorosulfonation of acetanilide, with *tert*-butylamine gives the corresponding sulfonamide (**34-2**). The acetyl group on nitrogen is then removed by heating with a strong base to give the aniline (**34-3**). Reaction of that with the fluoro anisaldehyde (**34-4**) gives imine (**34-5**), which incorporates the two adjacent aromatic rings characteristic of COX-2 inhibitors (note that the drawing does not indicate stereochemistry). Reaction of the imine with toluenesulfonyl isocyanate in the presence of potassium carbonate leads to what may be viewed as 2+3 cycloaddition of the nitrogen analogue of a ketene to form the imidazole ring (**34-6**). That ring is then chlorinated with *N*-chlorosuccinimide possibly to adjust the electron density on the heterocyclic ring. Heating this last intermediate (**34-7**) with acid removes the protecting group to give the free sulfonamide and thus **cimicoxib** (**34-6**) [36].

The nucleus of the one-time widely prescribed prescribed COX-2 inhibitor, **rofecoxib**, better known by its trade name Vioxx®, actually comprises a butenolide rather than a classical heterocycle. The drug was withdrawn from the market at full flood due to an unexpectedly high incidence of adverse cardiovascular side effects. The compound is included at this point to emphasize the breadth of the SAR for COX-2 anti-inflammatory agents. Reaction of phenylacetic acid (**35-1**) with ethyl bromoacetate in the presence of triethylamine leads to the formation of the ester (**35-2**). Treatment of that intermediate with a strong base generates a carbanion at the benzylic position; in an intramolecular reaction, this attacks the terminal ester carbonyl to yield the butenolide (**35-3**). Reaction of that compound with triflic anhydride converts the
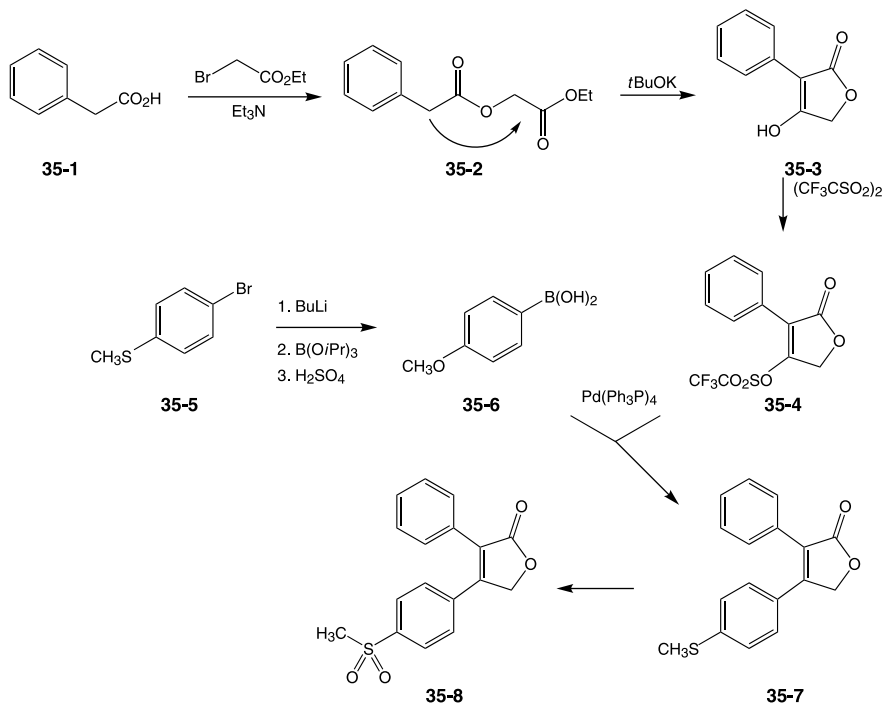
enolic ring hydroxyl to the corresponding triflate (**35-4**). In a convergent sequence, 4-bromothioanisole (**35-5**) is converted to the lithio reagent by exchange with butyl lithium. That intermediate leads to the boronate ester on reaction with tri-*iso*propyl. borate; exposure to a strong acid cleaves the ethers to afford the ogano-boric acid (**35-6**). A Heck-type reaction of (**35-6**) with triflate (**35-4**) in the presence of tetrakis-triphenylphosphine palladium leads to the displacement of the triflate; this then affords the coupling product (**35-7**). The oxidation of sulfur to a sulfone completes the synthesis of rofecoxib (**35-8**) [37].

8.3.2. Oxazoles, Isoxazoles, and Their Derivatives

An oxazole ring provides the base for an NSAID that combines the structural features found in both traditional anti-inflammatory agents and COX-2 inhibitors. The presence of the propionic acid side chain in the structure of the oxazole **oxaprozin** suggests that this compound was modeled on the then-known SAR of NSAIDs. The presence of the two aromatic rings on adjacent positions on the five-membered heterocycle seem to anticipate the more recent COX-2 inhibitors. Biological data, however, indicate that the compound shows the same lack of selectivity as the traditional NSAIDs. The synthesis of oxaprozin starts with the acylation of a benzoin derivative (**36-1**) with the half-ester acid chloride from succinic acid (**36-2**). Treatment of the resulting 1,4-dicarbonyl compound (**36-3**) with phosphorus oxychloride leads to the formation of the oxazole ring by a cyclodehydration reaction; this is a well-precedented standard method for forming five-membered heterocycles that in this case may well proceed via the enolized form (**36-4**) and then enol chloride (**36-4**). Saponification of the ester (**36-6**) affords **oxaprozin** (**36-7**) [38].
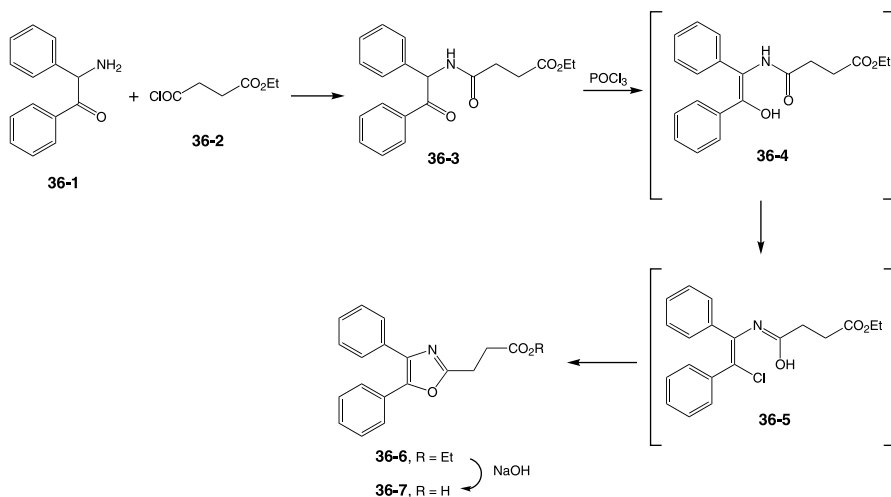
The strategy used for building the oxazole ring for the NSAID **romazerit** (**37-5**) relies on closing the ring at the nitrogen rather than the oxygen atom. The intermediate that incorporates the requisite oxygen atom is obtained by acylation of ethyl

2-hydroxyacetoacetate with 4-chlorobenzoyl chloride to give the di-ester (**37-1**), depicted in its enol form. Heating this compound with formamide in the presence of an acid probably leads initially to the replacement of the enol hydroxyl by ammonia, perhaps by a conjugate addition-elimination sequence (**37-2**). Imine formation between the amine and the benzoyl carbonyl group results in the formation of an oxazole ring and thus affords (**37-3**). The ester group is then reduced to a carbinol with lithium aluminum hydride and the resulting alcohol replaced by chlorine by means of thionyl chloride (**37-4**). Displacement of this activated halogen with the enolate obtained from ethyl 2,2-dimethylglycolate and sodium ethoxide leads to the displacement and formation of an ether bond. The ester on the newly connected side chain is then saponified to afford the corresponding acid and **romazerit** (**37-6**) [39].
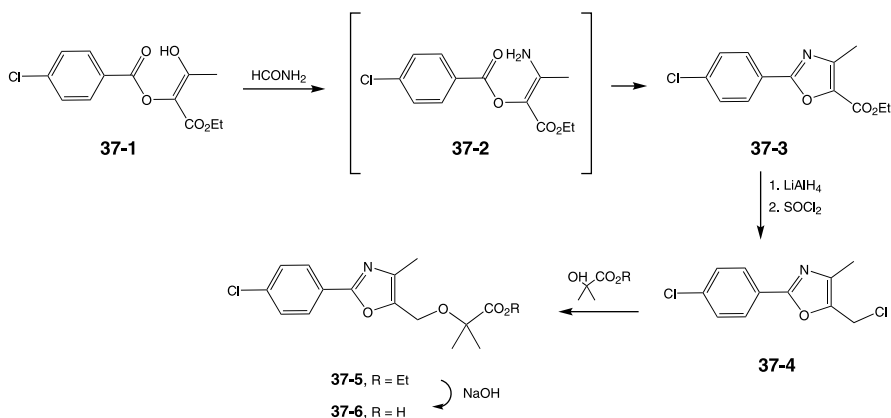
An oxazole substituted with a complex aminohydantoin side chain is described as a muscle relaxant. Imine formation between glyoxylic acid and aminohydantoin (**38-1**) results in the imino acid (**38-2**). Use of that intermediate to acylate the amine on 4-chloro-2′-aminoacetophenone (**38-3**) leads to the amide (**38-4**), which now includes a 1,4-dicarbonyl array. Treatment of the keto-amide with phosphorus
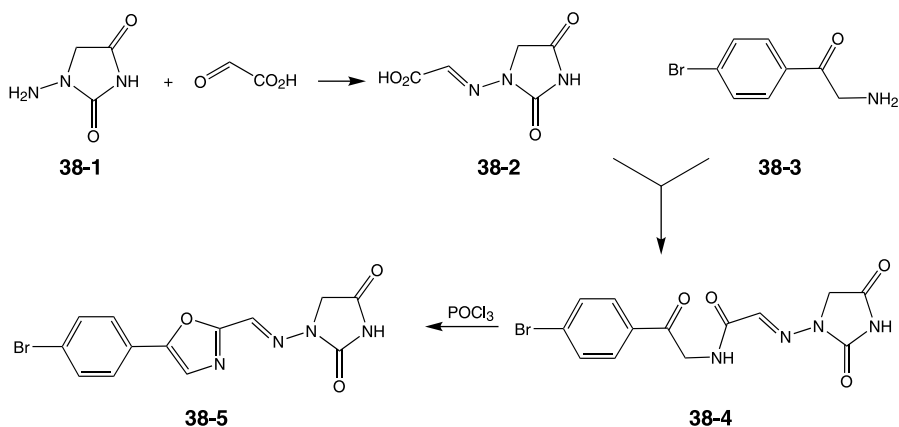
oxychloride leads to cyclodehydration and the consequent formation of an oxazole ring. There is thus obtained **azomolene** (**38-5**) [40].

The simple phenethylamine derivative amphetamine has well-recognized appetite suppressant and euphoriant activities; the latter has led to significant street use of the agent as an "upper." The SAR for this activity is sufficiently broad so that similar activity is shown by many compounds that show comparable spacing of an aromatic ring and an amino group. Reaction of phenylethanolamine (**39-1**) with cyanogen bromide can be envisaged as proceeding first to the corresponding cyanamide (**39-2**); internal attack by transient alkoxide oxygen on the nitrile triple bond leads to cyclization of the iminooxazolidine (**39-3**). Tautomerization to the endocyclic isomer gives the appetite suppressant agent **aminorex** (**39-4**) [41].
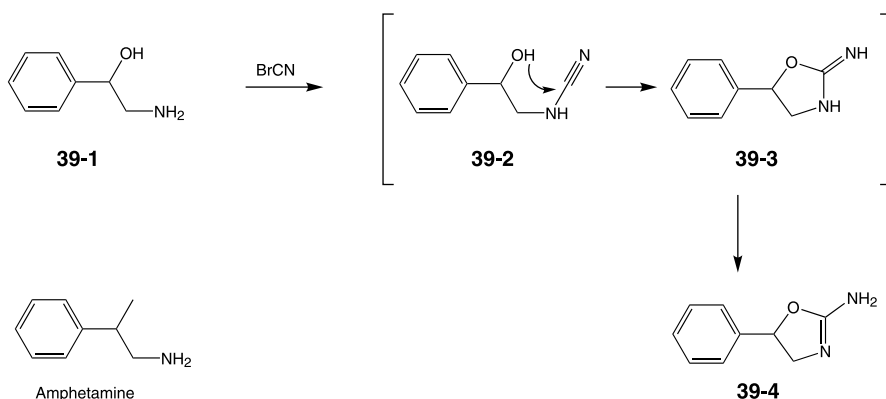
The dimethylaminooxazolidone derivative **thozalinone** (**40-3**) is described as an antidepressant. The synthesis of this agent again uses a cyanamide, provided in this case as a preformed reagent. Thus, reaction of alkoxide from ethyl mandelate (**40-1**) with *N,N*-dimethylcyanamide leads to the amidine (**40-2**) by addition to the nitrile. Internal displacement of the ester ethoxide group closes the ring to an oxazolidinone, forming the product (**40-3**) [42].
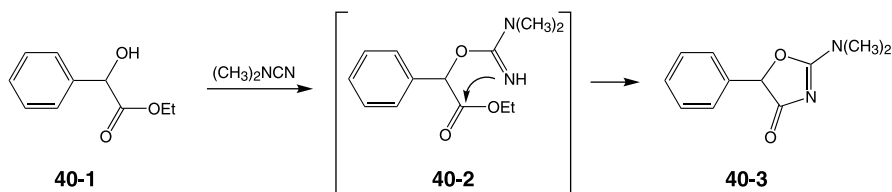
Fermentation products and their derivatives provide a large segment of today's very large collection of drugs for treating bacterial infections. Synthetic compounds that have no counterpart in nature, starting with the sulfonamides, comprise the other segment of that group. The excellent antibacterial activity obtained with quinolone carboxylic acids, developed from the 1980s onward (see Chapter 11), turned attention back to synthetic antibacterial compounds. A pair of oxazolidinone reported in the

mid-1990s may represent a new prototype for antibacterial agents. These agents are potent inhibitors of early bacterial protein synthesis and show wide-spectrum antibacterial activity, which extends to *Mycobacterium tuberculosis*. Nucleophilic aromatic displacement of fluorine in (**41-2**) with the *N*-carbobenzyloxy (CBZ) derivative of piperazine (**41-1**) leads to the arylpiperazine (**41-3**). The nitro group is then reduced to the corresponding aniline (**41-4**) and that acylated with phenyl chloroformate to give the urethane (**41-5**). Treatment of that product with butyl lithium gives the anilide anion. The first step when this anion is exposed to *R* butyryl glycidate (**41-6**) probably consists of an attack on the oxirane with consequent alkylation; the resulting anion then displaces phenoxide to form the oxazolidinone ring, with retention of the stereochemistry at the chiral center; saponification of the butyrate then gives the alcohol (**41-7**). The hydroxyl group is next converted to the mesylate by reaction with methanesulfonyl chloride. Displacement with potassium phthalimide then replaces the mesylate by nitrogen to afford (**41-8**). The imide protecting group is then removed by exchange with methylamine. Acylation with acetic anhydride gives the corresponding acetamide (**41-9**). Hydrogenolysis over palladium on charcoal serves to remove the carbobenzyloxy group to afford the secondary piperazine amine (**41-10**). Acylation with the benzyl ether from glycolyl chloride (**41-11**) followed by hydrogenolysis of the benzyl ether then affords **eperezolid (41-12)** [43].
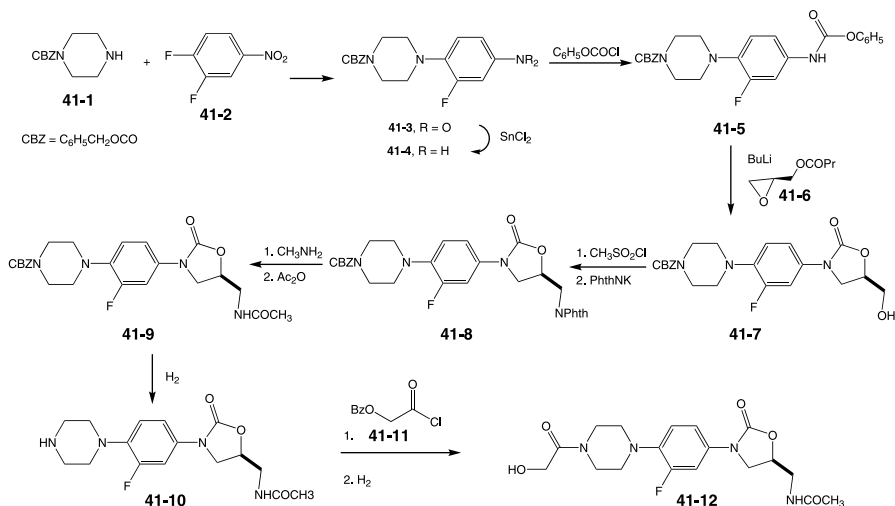
A more direct route is used to prepare the analogue in which the piperazine ring is replaced by morpholine. The sequence leading up to the oxazolidinone (**42-5**) is quite analogous to that above. The displacement of fluorine in (**41-2**) by morpholine gives the *N*-aryl morpholine (**42-2**). The nitro group is then reduced and the resulting aniline (**42-3**) is converted to its phenyl urethane (**42-4**). Reaction of the anion with *R* butyryl glycidol (**41-6**) leads to the key oxazolidinone (**42-5**). The alternate sequence for replacing the alcohol by an amine starts as above by its conversion to a mesylate; this is then displaced with sodium azide and the product hydrogenated to give the primary amine (**42-6**). Acylation of that product with acetic anhydride then affords **linezolid (42-7)** [43].
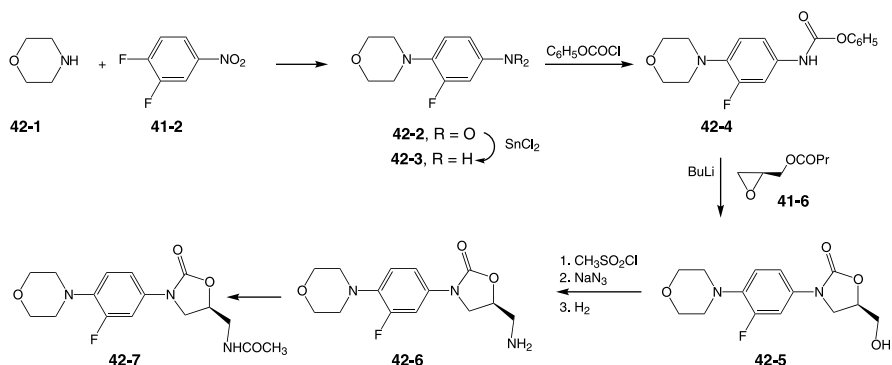
The structural requirements for anticonvulsant activity are quite broad. As noted in the next section, hydantoins are the best-known antiepileptic drugs. Selected succinimides, as noted earlier, and some oxazolidinediones show the same activity. The parent nucleus for the latter (**43-5**) was first prepared close to a century ago [44]. The original route involves the reaction of ethyl lactate (**43-1**) with guanidine; the first step probably involves the interchange of the ester with an acylated guanidine derivative such as (**43-3**). The addition of alkoxide to the imine followed by a loss of ammonia leads to the formation of the iminooxazolidone (**43-4**). The imino group is then hydrolyzed to a carbonyl and the resulting imide methylated by means of a base and methyl iodide to give the oxazolidinedione (**43-5**); the use of allyl bromide gives **aloxidone** (**43-7**). Further alkylation of this intermediate leads to a number of anticonvulsants. In a typical example, treatment of the carbanion from (**43-6**) and sodium ethoxide with methyl iodide gives **trimethadione** (**43-8**) [45].
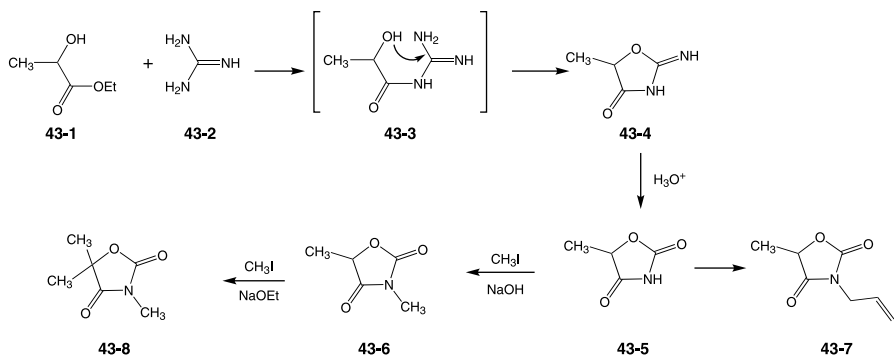
The classical method for preparing isoxazole involves the condensation of 1,3-dicarbonyl compounds with hydroxylamine, a reagent that contains the preformed N—O bond. The regiochemistry of the reactions can usually be rationalized by assuming that the first step involves imine bond formation at the more reactive carbonyl group. Thus, reaction of formyl ketone (**44-1**) with hydroxylamine gives

isoxazole (**44-3**), the product of the initial reaction at the aldehyde carbonyl group (**44-2**). Preparation of the second part of the compound in question, **disoxaril** (**44-6**), illustrates an alternative method for preparing oxazolines. An ester-amide interchange between ethyl 4-hydroxybenzoate and ethanolamine leads to the amide (**44-4**). The treatment of this intermediate with thionyl chloride probably proceeds first to the imino chloride; the addition elimination of the terminal side chain hydroxyl group leads to the formation of the oxazoline ring (**44-5**). Alkylation of the phenolate from (**44-6**) with bromide (**44-3**) then affords the antiviral agent **disoxaril** (**44-6**) [46].
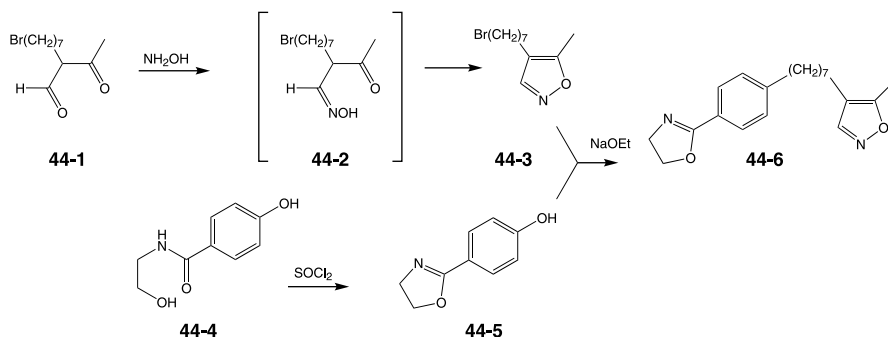
Isoniazide, the hydrazide of pyridine-4-carboxylic acid, is still, well over half a century after its discovery, one of the mainstays for the treatment of tuberculosis. Widespread use led to the serendipitous discovery of its antidepressant activity. This latter activity is retained when pyridine is replaced by isoxazole. The requisite ester (**45-4**) is obtained in a single step by condensation of the diketo ester (**45-1**), obtained by aldol condensation of acetone with diethyl oxalate, with hydroxylamine. One explanation of the outcome of the reaction assumes the first step to consist of conjugate addition-elimination of hydroxylamine to the enolized diketone to afford (**45-2**) an intermediate probably in equilibrium with the enol form (**45-3**). An ester-amide interchange of the product with hydrazine then affords the corresponding hydrazide (**45-5**); reductive alkylation with benzaldehyde completes the synthesis of **isocarboxazid** (**45-6**) [47].
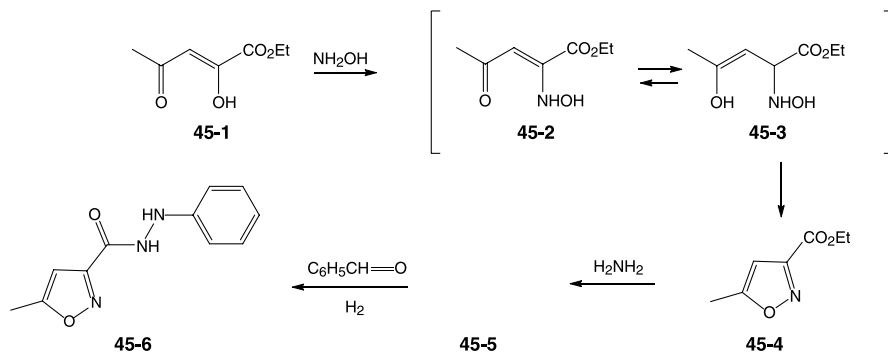
Fermentation products have proven to be an unusually rich source for leads for not only antibiotics, as noted previously, but also antineoplastic agents. This may be due at least in part to the fact that those products are elaborated by microorganisms as potential toxins toward other potentially threatening life forms. The antitumor activity of the amino acid derivative **acivicin** (**46-7**), elaborated by a *Streptomyces svicens*, is due to its interference with glutamate metabolism. The quite reactive imino chloro isoxazole moiety can be viewed as a surrogate for the second glutamate carboxylic acid. One total synthesis for this compound relies on a 1,3 dipolar cycloaddition reaction involving a chiral auxiliary for construction of the isoxazoline ring. The sequence starts by formation of the oxime (**46-1**), shown in cyclic form, from the D-ribose in which the hydroxyls at positions 3, 4, and 5 are protected. Reaction with paraformaldehyde leads to the transient nitrone (**46-2**). In a convergent synthesis, vinylglycine [48] is protected as its cyclic formaldehyde carbinolamine derivative (**46-3**). Treatment of that intermediate with (**46-2**) formed *in situ* leads to the 1,3-dipolar cycloaddition product (**46-4**) as a single chiral enantiomer. Exposure to formic acid cleaves the bond to the anomeric carbon to afford the bicyclic product (**46-5**). The all-important enol chloride is then introduced by treatment of this last product with *N*-chlorosuccinimide; there is thus obtained (**46-6**). Reaction of last intermediate with boron trichloride removes the remaining protecting groups to afford finally the free amino acid side chain; there is thus obtained **acivicin** (**46-7**) [49].
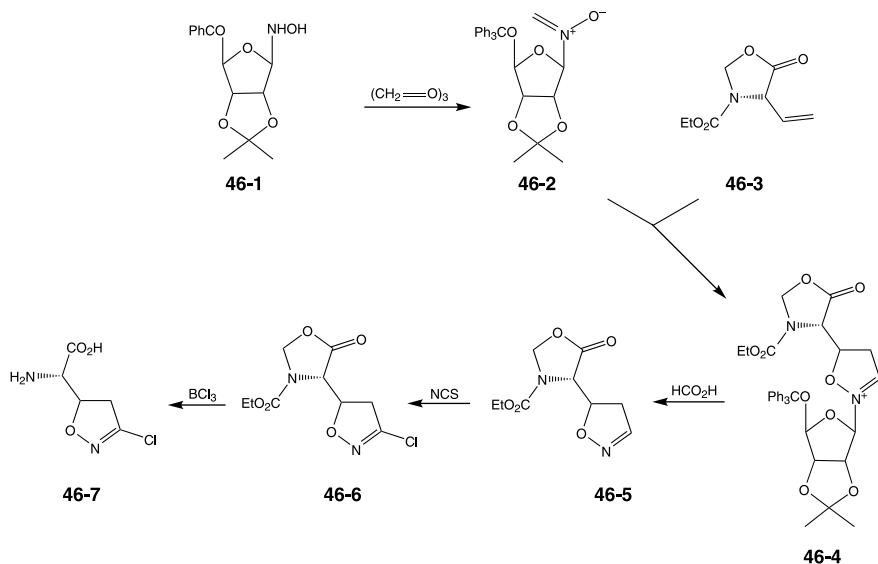
The antibiotic **cycloserine** (**47-7**), also originally isolated from fermentation broths, is still one of the important drugs used for controlling tuberculosis. This drug, interestingly, dates back six decades. The quite concise original synthesis for the compound involved racemic material possibly due to the difficulty in obtaining resolved starting materials in those days. The first step consists in protection of serine (**47-1**) as its xazoline (**47-3**) by reaction with the iminoether (**47-2**) obtained

from benzonitrile. An ester-amide interchange of the intermediate with hydroxyla-mine in the presence of sodium methoxide gives hydroxamic acid (**47-4**) on neutral-ization of the product. Reaction of that with anhydrous hydrogen chloride leads to a ring opening of the isoxazoline with a concurrent conversion of the latent hydroxyl group to a chloride (**47-5**), a reaction probably facilitated by the good leaving group properties of the amide function. Sodium hydroxide converts the hydroxamic acid to its anion; the negatively charged oxygen then displaces the chlorine internally to form the isoxazoline and thus afford the benzamide (**47-6**) [50]. Several steps were initially required to remove the amide; it was subsequently shown that **cycloserine (47-7)** could be obtained directly from the benzamide by treatment with trifluoroacetic acid.
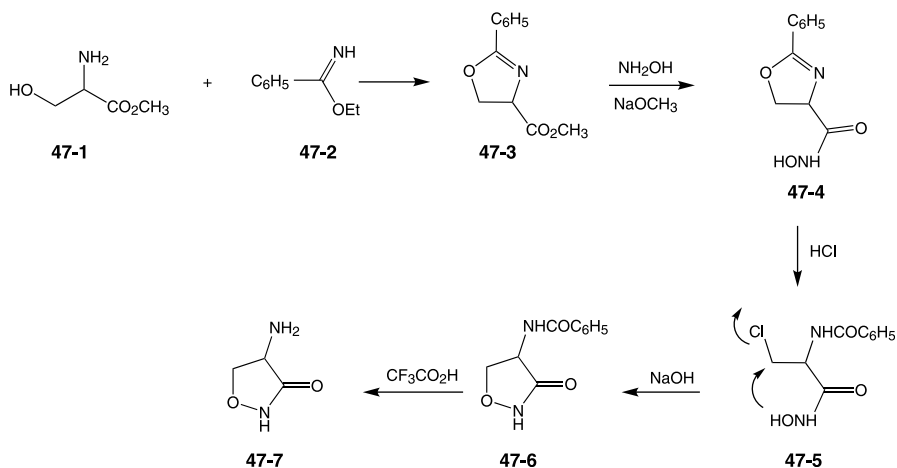
8.3.3. Imidazoles

Fully unsaturated imidazole rings feature prominently in several classes of therapeutic agents. The specific substitution pattern associated with each class of drugs suggests that these moieties play an important pharmacophoric role.

The antiprotozoal activity exhibited by nitroimidazoles bearing a substituent on the adjacent nitrogen prompted an enormous amount of work in this series. The extensive record of efficacy and safety of these compounds, called **metronidazole (48-5)**, has led to their being made available on a non-prescription basis for the treatment of vaginal trichomonal infections. The first step in the synthesis of this agent points up a structural ambiguity inherent in imidazoles. The starting material, 2-methylimidazole (**48-1**), exists as two freely equilibrating tautomers; the symmetry of the molecule results in their exact equivalence. The introduction of a second substituent, as, for example, a nitro group, leads to the production of two nonequivalent isomers; the product in fact consists of the pair of nitroimidazoles (**48-2**, **48-3**) that freely equilibrate. Treatment with a base under aprotic conditions has been found empirically to favor the formation of the anion (**48-4**) bearing the

charge adjacent to the nitro group. Treatment with ethylene chlorohydrin leads to the alkylation and formation of **metronidazole** (**48-5**) [51].
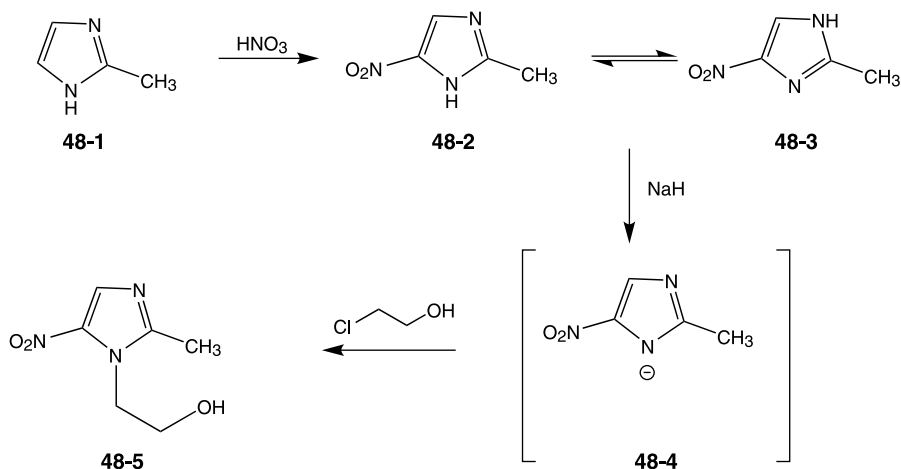
The same regiochemistry is observed when nitroimidazole (**48-2, 48-3**) acts as a nucleophile in unionized form. Thus, the reaction of a compound with benzoyl-aziridine (**49-1**) in the presence of boron trifluoride probably involves an initial salt formation with an amide; attack by the imidazole results in a ring opening and the formation of the alkylated product (**49-2**); the free primary amine (**49-3**) is obtained on basic hydrolysis. Acylation of the primary amine with methyl thiochloroformate gives the corresponding thiourethane, **carnidazole** (**49-4**) [52].
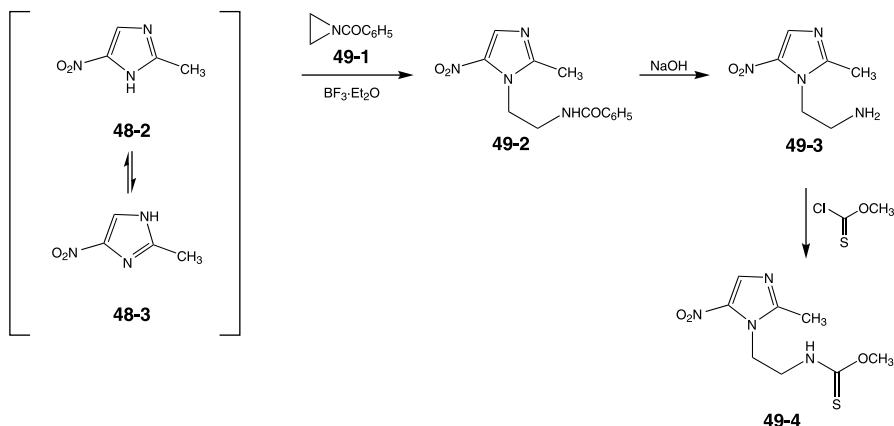
The *N*-methyl group in the starting material (**50-1**) for the antiprotozoal compound **ronidazole** (**50-3**) in essence locks that compound into a single isomeric form. Nitration occurs predominantly at the presumably more electron-rich position to give the 5-isomer; saponification of the acetate protecting group then leads to the

free alcohol (**50-2**). Reaction of the alcohol with potassium isocyanate in hydrofluoric acid gives the product from the reaction of the alcohol with isocyanic acid generated *in situ*, giving **ronidazole** (**50-3**) [53].
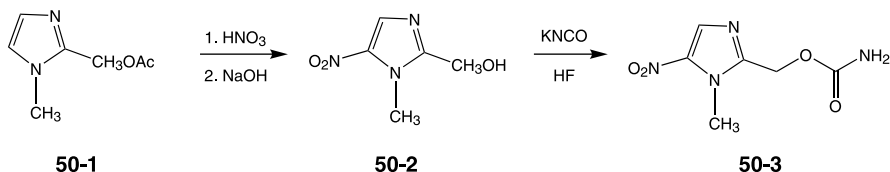
The preparation of the antitrichomonal agent substituted with an aromatic ring on the imidazole starts with the condensation of the iminoether (**51-1**) from 4-fluorobenzonitrile with the dimethylacetal (**51-2**) from 2-aminoacetaldehyde; the reaction can be envisaged to involve the initial formation of an amidine by exchange of the ether methoxyl with the primary amine; hydrolysis of the acetal groups under reaction conditions would give the imine-aldehyde that then cyclizes to (**51-3**) by Schiff base formation. Nitration gives the usual mixture of isomers, only one of which (**51-4**) is shown. A special stratagem is required to make up for the tendency of the imidazole pair to give the undesired alkylation product; this consists in essence of initially introducing an easily removable alkyl group. Thus reaction with methylchloromethyl ether gives the imidazole (**51-5**). The future hydroxyethyl side chain is then incorporated by alkylation of the second nitrogen with the highly reactive fluoroborate from the cyclic ethylene acetal of acetic acid; this yields the unstable quaternary salt (**51-6**). Heating in pyridine leads to cleavage of the methoxymethyl group; this results in the net removal of one of the nitrogen alkyl groups leaving the hydroxyethyl at the desired position. Hydrolysis of the acetate group in the intermediate completes the synthesis of **flunidazole** (**51-7**) [54].
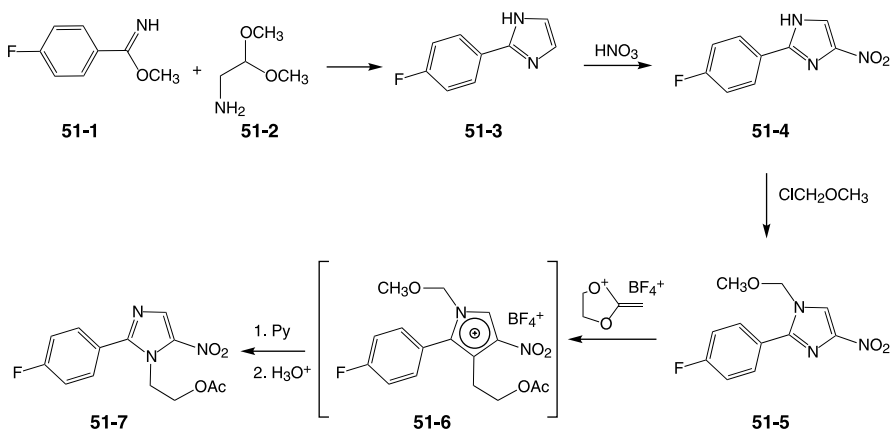
The very simple nitroimidazole **azomycin** (**52-2**) is one of the very early compounds uncovered by the extensive search for antibacterial agents produced by *Streptomyces* fermentation. Its development as an antibiotic drug was probably

precluded by its toxicity. The **mycin** ending for the name, it might be noted, indicates the fact that the compound comprises a *Streptomyces* fermentation product. A slightly circuitous route was used for its total synthesis since is not accessible by direct nitration of imidazole. The key 2-aminoimidazole (**52-1**) is obtained by condensation of cyanamid with the acetal from 2-aminoacetaldehyde (**51-2**). The amine is then diazotized and the diazonium salt replaced by nitro by Sandmeyer reaction with sodium nitrite in the presence of cuprous chloride [55].

Ionizing radiation, for example, X-rays, is one of the oldest and still extensively used methods for treating cancer. The generalized organ and tissue toxicity of this form of treatment puts a premium on delivering the radiation preferentially to the cancerous tumors. It was found adventitiously that 2-nitroimidazoles such as **metronidazole** increased the sensitivity of solid tumors to the cell killing effect of radiation. These agents seem to be particularly effective in the oxygen deficient environment found in solid tumors. **Azomycin** (**52-2**) provides the starting material for one of these agents. Thus, alkylation of that compound with ethyl chloroacetate in the presence of sodium hydroxide gives the ester (**52-3**). Ester interchange with ethanolamine gives the corresponding amide, **etanidazole** (**52-4**) [56].
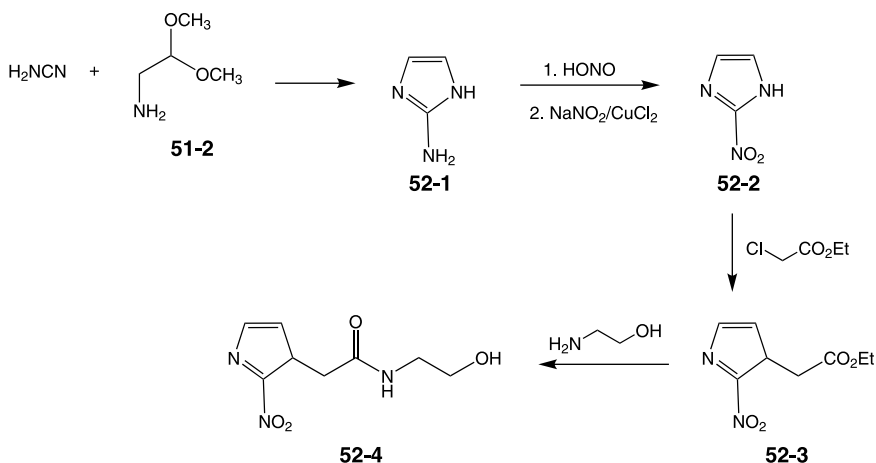
The synthesis of the antifungal agent **ethonam** (**53-6**) illustrates yet one more method for building imidazole rings. Reaction of 5-aminotetralin (**53-1**) with ethyl chloroacetate under carefully controlled conditions leads to the monoalkyl product; this is then converted to the formamide (**53-2**) with formic acid. Condensation of that intermediate with ethyl formate in the presence of sodium ethoxide gives the hydroxymethylene derivative (**53-3**). Treatment with isothiocyanic acid from sodium isothiocyanate and mineral acid can be envisaged as involving the initial replacement of the hydroxyl group in (**53-3**) by a conjugate addition-elimination sequence to give an intermediate such as (**53-4**). Internal exchange of the formyl group with the adjacent thiocarbonyl group will lead to a thioimidazoline; this can then tautomerize to the imidazothiol (**53-5**). Desulfurization with Raney nickel then gives **ethonam** (**53-6**) [57].
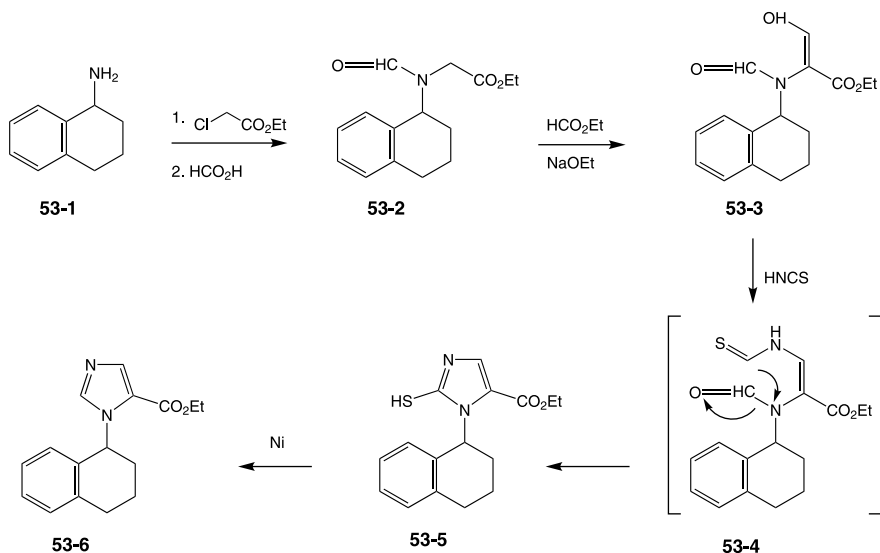
Otherwise unsubstituted imidazole rings, and to a lesser extent 1,2,4-triazole rings, covered later, form an essential part in the most important class of antifungal agents, the so-called conazoles. The selective toxicity of these drugs depends on the fact that they inhibit fungal enzymes responsible for the biosynthesis of ergosterol. This steroid plays an important structural role in the organism's cell membrane. Cholesterol, produced by a different pathway, fulfills that role in animal species. Most conazoles possess, in addition to the heterocyclic ring, one or more chlorinated aromatic rings; very wide latitude seems to exist as to the skeleton that connects those moieties. The agents discussed below constitute a very small sample of the enormous number of antifungal compounds that have been described.

Bromination of 2,4-dichloroacetophenone provides the α-bromoketone (**54-1**), key to the synthesis of a number of conazoles. The corresponding α-imidazo derivative
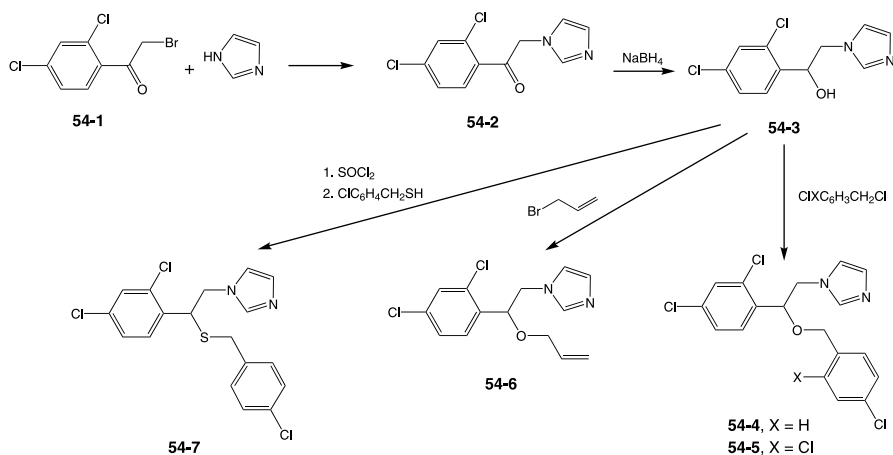
(**54-2**) is obtained by displacement of halogen by imidazole; the carbonyl function is then reduced to the alcohol (**54-3**), typically with sodium borohydride. The displacement of chlorine from α,4-dichlorotoluene with the alkoxide from (**54-3**) affords the antifungal agent **econazole** (**54-4**) [58]; the analogous reaction using α,2,4-trichlorotoluene gives **miconazole** (**54-5**) [58]. The bioisosteric relation of oxygen and sulfur apparently maintains in the case of the conazoles; thus, conversion of the hydroxyl in (**54-3**) to chlorine followed by displacement with 4-chlorobenzylthiol as its anion gives the antifungal agent **sulconazole** (**54-7**) [59]. The second halogenated ring is apparently not absolutely required for activity; thus reaction of the alkoxide from (**54-3**) with allyl chloride gives **enilconazole** (**54-6**) [58].

An imine moiety can, interestingly, be interposed in the ether linkage used to connect the two halogenated aromatic rings. The requisite oxime (**55-1**) is obtained in a straightforward fashion by reaction of imidazo acetophenone (**54-2**) with hydroxylamine; alkylation with α,2,3-trichlorotoluene leads to **oxiconazole** (**55-2**) [60].
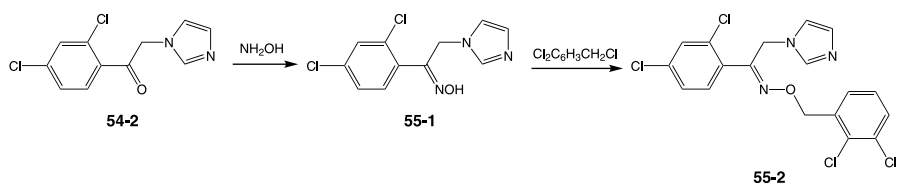
The orally active antifungal agent **ketoconazole** (**56-6**), had been widely used in the treatment of opportunistic fungal infections in AIDS patients until the advent of newer, more effective drugs. The synthesis of this agent starts with the formation of the acetal (**56-2**) from 2,4-dichloroacetophenone (**56-1**) and glycerol. Reaction with bromine, which may well proceed via a small amount of ketone in equilibrium with the acetal, gives the intermediate (**56-3**). The aliphatic halogen is then displaced with imidazole and the free hydroxyl group converted to a mesylate leaving group by reaction with methanesulfonyl chloride (**56-4**). Displacement of the mesylate with the phenoxide from the treatment of a side chain (**56-5**) with a base affords **ketoconazole** (**56-6**) [61].
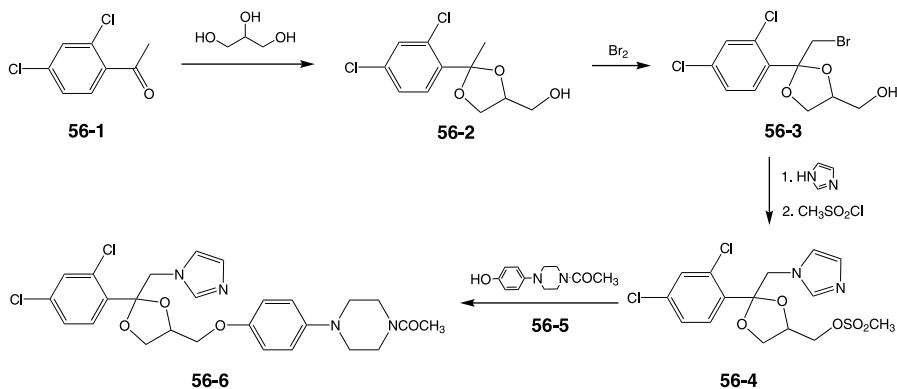
The structural latitude that exists in this series is further illustrated by a series of antifungal agents that differ markedly in structure from the first-introduced drugs. Several of the compounds that follow include linkages that would seem to be subject to easy hydrolysis. Activity is, for example, retained when the benzene ring is replaced by thiophene and a hydrazide provides the linkage. The intermediate (**57-2**) is obtained by displacement of halogen in (**57-1**) with imidazole; condensation with 2,6-dichlorophenylhydrazine gives the hydrazone **zinoconazole** (**57-3**) [62].
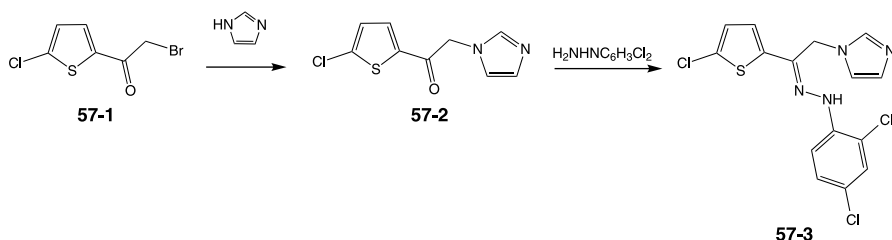
The starting material (**58-1**) for **lanoconazole** (**58-4**) can be obtained by alkylation of imidazole with chloroacetonitrile. Reaction with carbon disulfide proceeds at the activated methylene group in the side chain to afford the condensation product (**58-2**), depicted as the initially charged form. That di-anion intermediate is next treated with the *bis*-mesylate (**58-3**) from 2-chlorophenylethylene glycol. Sequential displacement of the mesylate groups by the sulfides forms the dithiolane ring affording lanoconazole (**58-4**) [63], apparently as a single geometric isomer.
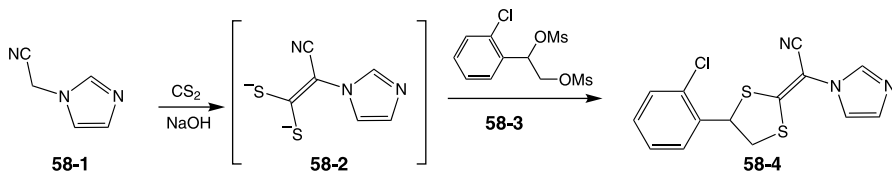
An iminoether bond forms the link between large parts of the molecule in yet another of the unusual conazoles. Bromination of 2,4-dichloropropiophenone (**59-1**) affords the corresponding bromide (**59-2**). Treatment with imidazole displaces the activated halogen atom to afford the intermediate (**59-3**). The second major fragment
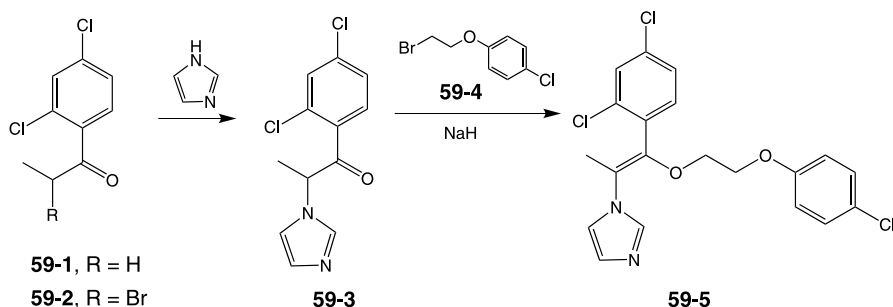
(**59-4**) could be obtained by one of several methods, as, for example, alkylation of 4-chlorophenol 2-bromoethanol. Reaction of the enolate from the ketone with the side chain fragment (**59-4**) yields the antifungal agent **omoconazole** (**59-5**) [64].

The topical antifungal **bifonazole** (**60-2**) dispenses with virtually all but the imidazole ring; the intermediate (**60-1**) is obtained by sequential reduction of 4-phenyl-benzophenone and then reaction of the alcohol with thionyl chloride. Displacement of chlorine by imidazole gives (**60-2**) [65].

60-1   **60-2**
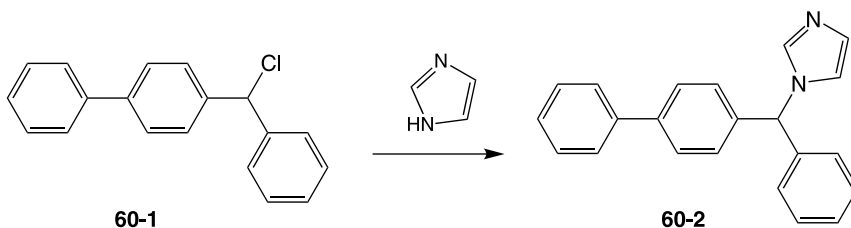
The pivotal role of histamine (**61-1**) in allergic reactions was recognized as early as 1911. Further pharmacological studies uncovered the role of that compound in the release of gastric acid. The first antiallergic drugs, such as **diphenhydramine** (**61-2**), were available some three decades later. Neither that class of drugs nor its more effective tricyclic successors, which are discussed in Chapter 13, however, had any effect on histamine-mediated gastric acid secretion. Detailed research that involved the study of a large number of analogues of histamine led to the recognition of two separate populations of receptors for that agent: Interaction with the so-called H_1 receptors leads to allergic manifestation; gastric acid secretion, on the other hand, involves activation of the H_2 receptors. The lack of effect of classical then-available antihistamines on acid secretion could thus be attributed to their selective binding to H_1 receptors. A direct consequence of this research was the development of a series of H_2 receptor antagonists that inhibit acid secretion and have thus found widespread use in treating gastric ulcers. The first of these drugs to reach the market, **cimetidine** (**64-3**), was developed by the laboratory responsible for the work that resulted in the recognition of two separate receptors; this agent is now, because of a long record of freedom from side effects, available as a nonprescription drug. The follow-on furan competitor, **ranitidine** (**4-5**), described earlier in this chapter, was approved for over-the-counter sales about a year later.

61-1
Histamine

61-2
Diphenhydramine
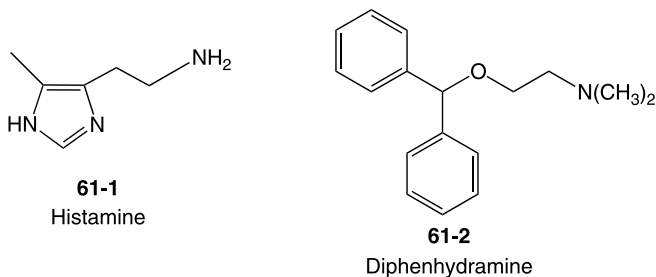
The structure of the first H_2 antagonist, **burimamide (62-4)**, bears a close structural resemblance to that of histamine itself, differing only by the presence of an extended side chain that bears a slightly acidic thiourea group instead of basic nitrogen. The synthesis starts with the reaction of the diaminoalcohol (**62-1**) (itself obtained by reduction of the corresponding ester) with ammonium isothiocyanate. The initial step probably consists in the formation of a thiourea at the amino group adjacent to the alcohol; the hypothetical aldehyde from the oxidation of that function could then from an imine with ammonia; cyclization would then lead to the observed thioimidazoline (**62-2**). Treatment with iron powder removes the sulfur reductively so as to form the imidazole (**62-3**). Reaction with methyl isothiocyanate gives the corresponding thiourea, **burimamide (62-4)**.
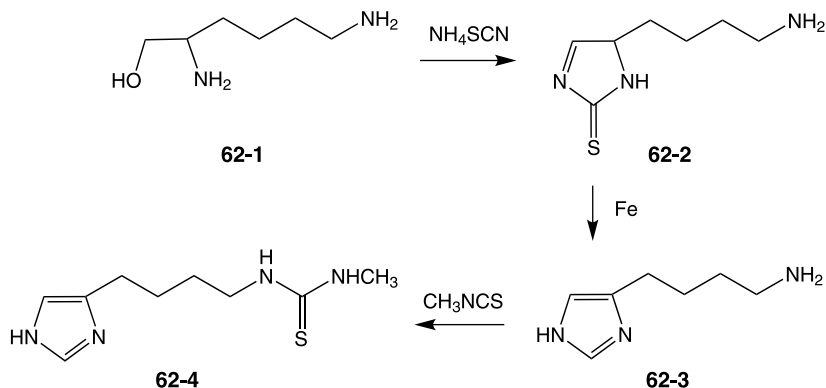
Side effects noted with that agent in the clinic led to its abandonment. The preparation of the second compound illustrates another method for forming imidazole rings. Thus, the first step in the reaction of 2-chloroacetoacetate, shown as its enolate (**63-1**), with formamide can be envisaged to involve the formation of the intermediate (**63-2**) by an addition-elimination sequence; the enolic β-hydroxyl can then undergo a similar displacement. Loss of one formyl group followed by internal imine formation will then lead to an imidazole ring to afford (**63-3**). The carbethoxy group in that intermediate is then reduced to the corresponding alcohol (**63-4**) by
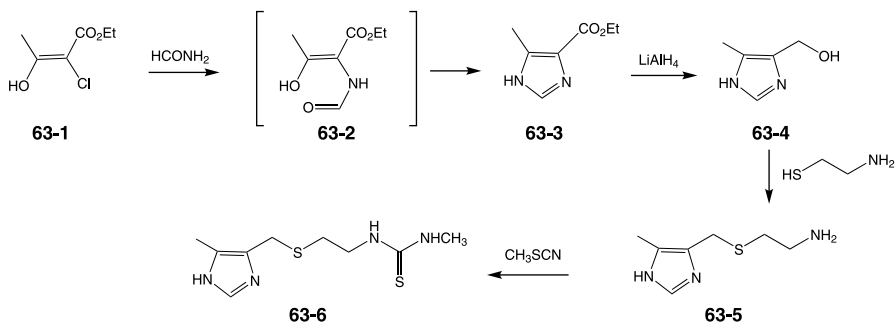
means of lithium aluminum hydride. Treatment of that product with the cysteamine in the presence of hydrogen hydrochloride leads to the displacement of the benzylic type alcohol by sulfur to give the thioether (**63-5**). Condensation of the product with methyl isothiocyanate gives **metiamide** (**63-6**).

The fact that this agent caused similar side effects as its predecessor led to the search for a replacement for the thiourea group. The cyanoguanidine function that was eventually found to be suitable is bioisosteric with thiourea in that the cyano group reduces the basicity of the guanidine; the nitrovinyl amidine in ranitidine serves the same function. Reaction of the metiamide intermediate (**63-5**) with dimethythiocyanoimidocarbonate (**64-1**) leads to the replacement of one of the methylthio groups by the side chain amino group to afford the intermediate (**64-2**). Treatment of that with methylamine under somewhat more strenuous conditions replaces the remaining methylthio group to afford **cimetidine** (**64-3**) [66,67].
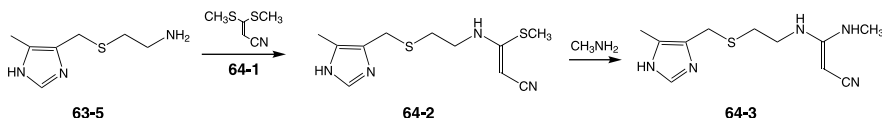
The surprising fact that biological activity is sometimes maintained when a methyl group is replaced by propargyl provides a fast route to analogues that are distinct for the purposes of patents. The preparation of the propargyl derivative of cimetidine also changes the order of the steps in the synthesis. Thus, reaction of cyanoamidine (**65-1**) (obtained by treatment of the thiocarbonate above (**64-1**) with propargylamine) with cysteamine leads to the replacement of the second methylsulfide group and the formation of the cyanoguanidine (**65-2**). Reaction of chloromethyl imidazole (**65-3**), obtained from (**63-4**), with the side chain as its mercaptide leads to the replacement of halogen and the formation of the histamine H_2 **etintidine** (**65-4**) [68].
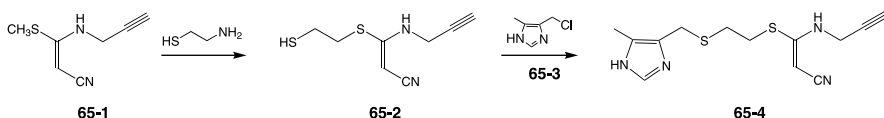
Work from other laboratories, some of which is discussed in Chapter 9, later showed 2-aminopyrimidones could fulfill the same functions in histamine H_2 blockers as do thioureas and modified guanidines in the initial compounds; many of these agents are interestingly devoid of histamine-like nuclei. **Oxmetidine** (**66-2**) represents a hybrid in that it includes moieties from both series. The pyrimidone-2-thiol (**66-1**) is prepared in a manner analogous to that which will be described in Chapter 9 for **lupitidine**; condensation of this with the intermediate (**63-5**) leads to the replacement of the thiol by the terminal amino group. There is thus obtained **oxmetidine** (**66-2**) [69].
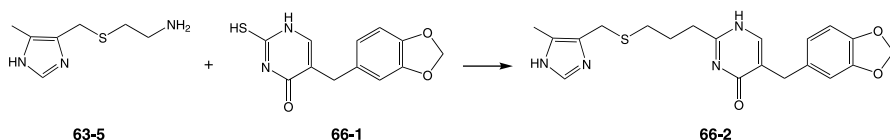
One of the key findings in the chain of events that led to the discovery of COX-2 anti-inflammatory agents [70] consisted in the observation of platelet anti-aggregation activity of the di-anisylthiazole **itazigrel** (**101-3**). It was not recognized at the time that the activity was due to the inhibition of a variant cyclooxygenase. A compound in which sulfur in the five-membered ring of itazigrel is replaced by nitrogen exhibits much the same activity. An alternative approach to building the imidazole ring involves adding nitrogen in the form of an ammonium salt and the carbonyl component that will form the carbon atom at the 2 position as a separate component. The reaction of dibenzyl (**67-1**) with ammonium acetate and trifluroacetaldehyde ethyl hemiacetal (**67-2**) is probably preceded by equilibration of the latter two reagents to form (**67-3**). Condensation of that with one of the carbonyl groups will lead to the intermediate (**67-4**); the remaining nitrogen can be added either by further acetal exchange or by imine formation. Cyclization then affords the anti-inflammatory agent **flumizole** (**67-5**) [71].
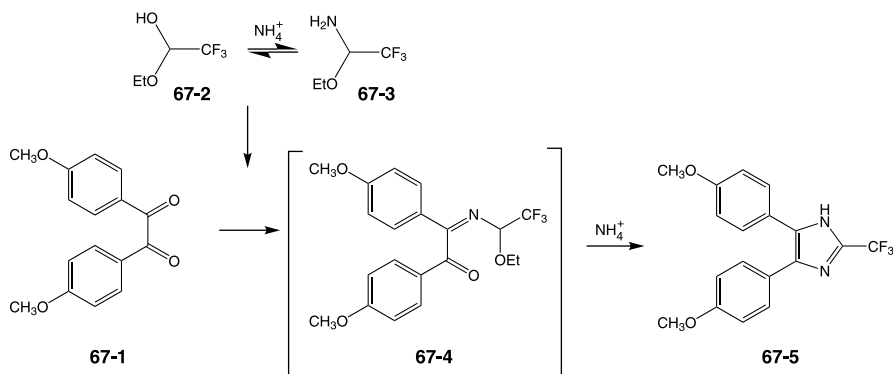
A similar approach is used for **trifenagrel** (**68-1**), an antithrombotic agent whose structure includes the 1,2-diaryl heterocyclic array common to COX-2 inhibitors. Alkylation of the phenoxide from salicylaldehyde with 1,2-dibromoethane affords the bromoethyl ether (**68-1**); displacement of halogen with dimethylamine gives the corresponding basic ether (**68-2**). This intermediate is then condensed with dibenzyl (**68-3**) in the presence of ammonium acetate, which results in the formation of an imidazole ring by a process directly analogous to that above, giving **trifenagrel** (**68-4**) [72].
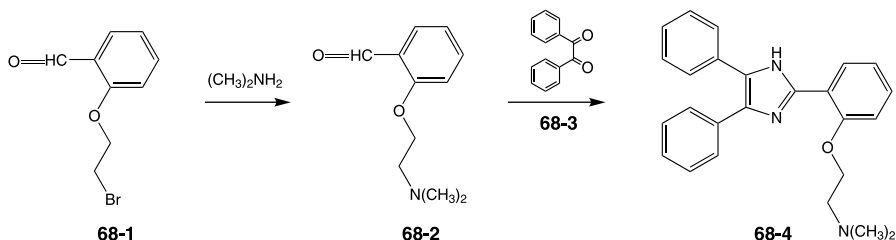
The imidazole **lofemizole** (**69-3**) is also described as an anti-inflammatory agent and it, too, has been found to be a COX inhibitor; the selectivity of this highly

simplified structure appears to not have been reported. The agent is obtained in a single step by reaction of the hydroxypropiophenone (**69-1**) with formamide [73]. This transformation, which is reminiscent of that described above for the **metiamide** intermediate (**63-2**), can be rationalized by assuming that the first step is the displacement of hydroxyl by the amide to form (**69-2**). Imine formation from the ketone with a second mole of formamide, followed by cyclization with loss of formate, would then give the observed product.
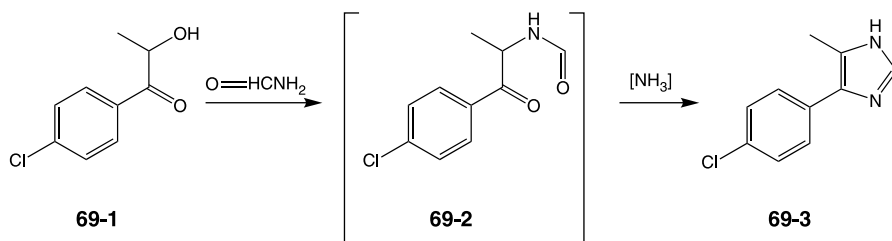
Compounds that display either agonist or antagonist activity of the β-adrenergic system consist of the arylethanolamines or aryloxypropanolamines discussed in Chapter 2; few, if any, other structural types show that activity. The situation is quite different for the α-adrenergic system. Though epinephrine is the endogenous agonist, some of the most potent synthetic agonists for this receptor consist of imidazolines. A few imidazoles also show α-adrenergic activity. It might be noted that the recent identification of α-receptor subtypes has led to work aimed at developing compounds with selectivity for such discrete receptor subclasses. The imidazole **atipamezole** (**70-6**), for example, has been found to display α_2 antagonist and nonopioid analgesic activity. Successive alkylation of the anion obtained from allylmethyl ketone (**70-2**) and lithium diisopropylamide by the by dibromide (**70-1**) leads to spirocyclization and formation of the indan (**70-3**). Reaction with bromine interestingly proceeds on the carbonyl methyl group rather than the olefin to provide the bromoketone (**70-4**). Treatment of the compound with formamide proceeds to form the imidazole (**70-5**), very much as in the case of the 2-hydroxyketone above. Catalytic reduction of the pendant vinyl group affords **atipamezole** (**70-6**) [74].
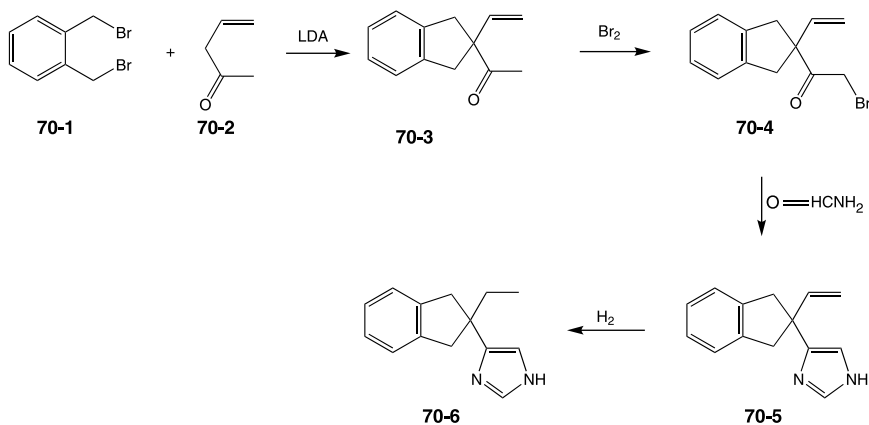
The benzodioxan nucleus has itself also been associated with α-adrenergic agents; it is of interest that combining this moiety with an imidazole leads to an α_2-agonist. Reaction of iminoether (**71-1**), obtained by treatment of the corresponding nitrile with ethanolic hydrogen chloride, with the diethylacetal of aminoacetaldehyde probably proceeds initially to give the amidine replacement product as a transient intermediate. Internal imine formation with the aldehyde or, alternatively, replacement of acetal groups by amino leads to cyclization and the formation of the imidazole intermediate (**71-2**). Alkylation of the salt obtained by means of sodium hydride with ethyl iodide gives **imiloxan** (**71-3**) [75], a compound that displays antidepressant activity.
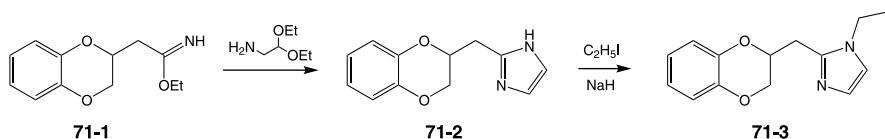
The nucleoside adenosine exerts a protective role on the heart, particularly in case of cardiac infarction. The A_1 adenosine receptors fulfill a largely inhibitory role in that organ. Research has thus focused on agonists with structures based on adenosine itself as agents that will overcome responses due to inappropriate excitation such as tachycardia and some arrhythmias. A series of compounds based on the full purine nucleus are to be found in Chapter 15. An analogue in which the fused six-membered ring of the purine is omitted has shown cardioprotective activity in the clinic. Reaction of 2-bromo tribenzoyl ribose (**72-1**) with 1,2-diaminomaleionitrile (**72-2**) results in the displacement of the anomeric halogen by one of the amino groups and the formation of the aminosugar (**72-3**) largely as the β anomer. Treatment of this product with methyl orthoformate in the presence of a base leads to the replacement of the alkoxy groups in orthoformate by the adjacent amines, resulting in the formation of the imidazole ring (**72-4**). Reaction with alkoxide then interestingly converts the nitrile nearest the sugar to an iminoester; the benzoyl groups are cleaved in the process to afford (**72-5**). Hoffman rearrangement in the presence of a bromine and a base converts the iminoester to the corresponding primary amine (**72-6**). Basic hydrolysis then converts the remaining nitrile to an amide, affording **acadesine** (**72-7**) [76].
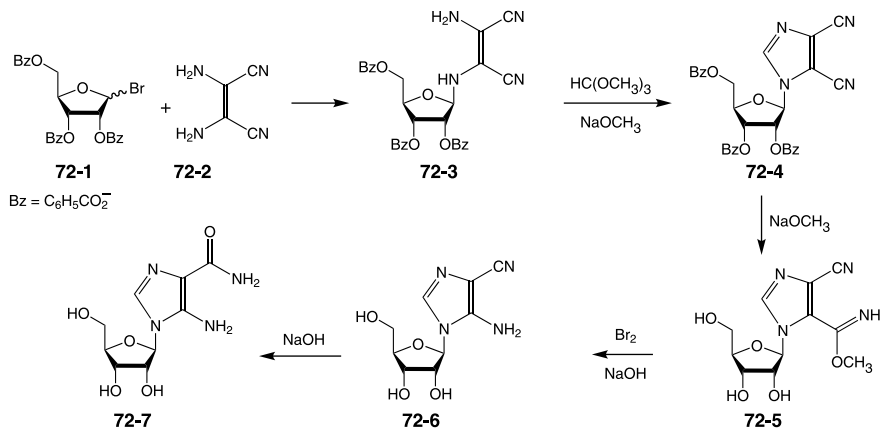
The conazole antifungal agents, as noted previously, shut down the synthesis of the steroids that play a crucial role in the organisms' existence. An imidazole that bears a more than passing structural similarity to the conazoles inhibits the mammalian enzyme lanosterol 14α-demethylase and, as a result, the synthesis of cholesterol. The compound has, as a result, been investigated as an oral hypocholesterolemic agent. Swern oxidation of the hydroxyl group in (**73-1**) affords the corresponding ketone (**73-2**). Acetal exchange with the chiral acetonide (**73-3**) leads to the formation of the acetal (**73-4**) as a mixture of diastereomers. The desired isomer (**73-4**) is separated by chromatography. Treatment of this last intermediate with 4-aminothiophenol (**73-5**) in the presence of a base leads to the displacement of the tosylate group and the incorporation of this last moiety as a thioether. There is thus obtained **azalanstat** (**73-6**) [77].
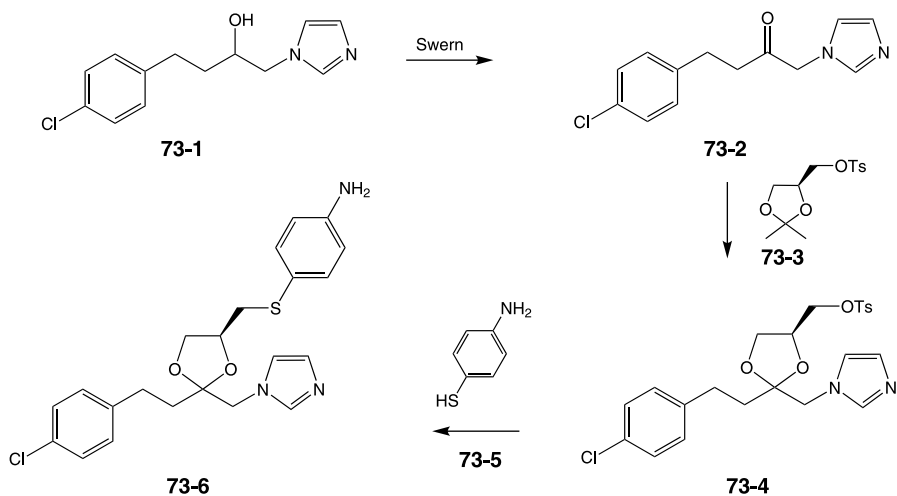
A structurally related compound with a shortened chain between substituents shows markedly different activity. This agent, **erbulozole**, inhibits the function of the cellular microtubules that play a critical role in cell division. The compound has thus been studied as a potential antitumor agent. The starting ketone (**74-1**) can, in principle, be obtained by alkylation of imidazole with bromoacetophenone. Reaction of this compound with glycerol proceeds to form the five-membered acetal (**74-2**) with a pendant hydroxymethyl group as a diastereoisomeric mixture. This intermediate is then esterified with benzoyl chloride. The derivative whose stereochemistry corresponds to (**74-3**) is then separated from the mixture. The benzoyl group is next saponified and the thus-obtained alcohol converted to a leaving group by reaction with methanesulfonyl chloride (**74-4**). Reaction with the urethane (**74-5**) from 4-aminothiophenol affords **erbulozole** (**74-6**) [78].
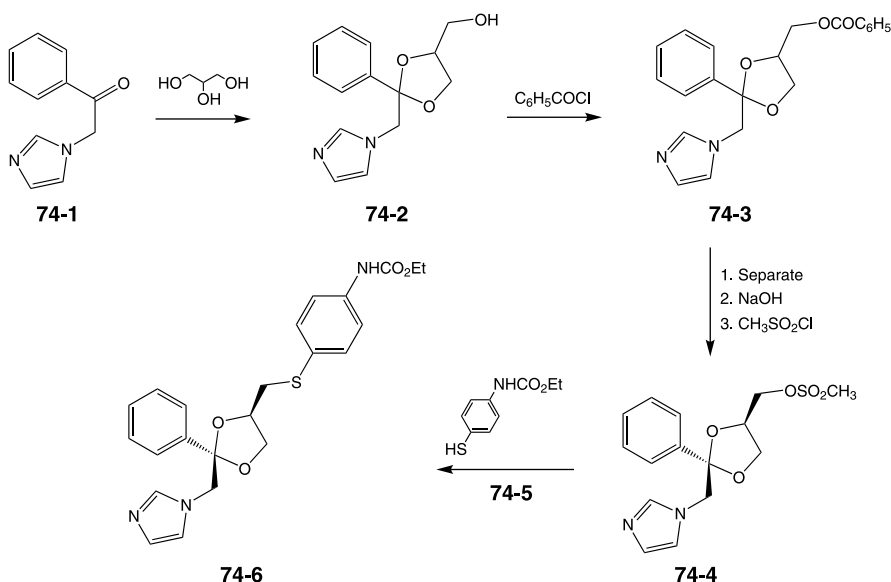
Histamine H_3 receptors have been found to modulate the release of neurotransmitters involved in alertness in cognitive function, such as acetylcholine, dopamine, and serotonin. Compounds that interact with those receptors favor the release of the neurotransmitters and result in increased alertness in animal models. Such agents would hold promise for the treatment of attention deficit syndrome and related conditions as well as possibly Alzheimer's disease. The first step in the synthesis toward the antagonist **cipralisant** (**75-7**) comprises the separation of the enantiomers of the carboxylic (**75-1**). To this end, the acid is reacted with a chiral sultam derived from camphor. The resulting diastereomers (**75-2**) are then separated by chromatography. Each of the diastereomerically pure derivatives, only one of which is shown, is then treated in the cold with diisobutyl aluminum hydride (DiBAL) to afford the corresponding aldehyde (**75-3**). Reaction with the anion from C-trimethylsilyl diazomethane gives the acetylene (**75-4**) in a single step. The chain is then extended by reaction of the acetylide anion with the triflate derivative from 3,3-dimethyl butanol (**75-5**). Exposure to
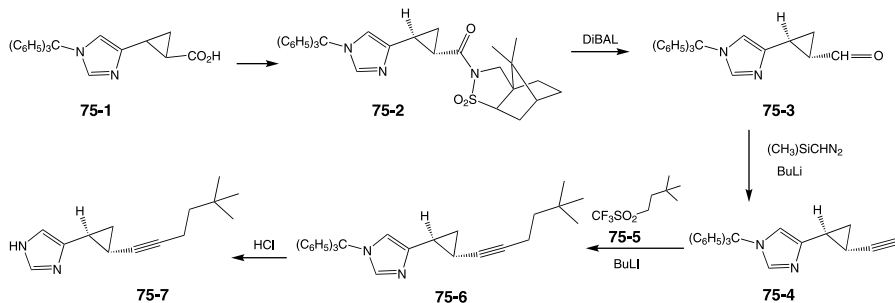
a strong acid serves to remove the triphenylmethyl protecting group on nitrogen (**75-6**). This last step affords cipralisant (**75-7**) [79]. The absolute stereochemistry was derived from X-ray structure determination of one isomer of the sultam (**75-2**).

The three-part so-called cocktail used to treat HIV positive patients typically comprises a proteinase inhibitor such as those discussed in Chapter 1, a nucleoside-based reverse transcriptase inhibitor such as those discussed in Chapter 9, and a non-nucleoside inhibitor of reverse transcriptase (NNRTI). Most of the compounds in the first two classes share a good many structural features with other agents in the class. The chemical structures of the various NNRTIs, on the other hand, have little in common. **Capravirine** (**76-11**) is notable in the fact that it fails to include any of the fused ring systems that provide the nucleus for other compounds in this class. Chlorination of 3-methylbutyraldehyde (**76-1**) provides one of the components for building the imidazole ring (**76-2**). For bookkeeping purposes, the condensation of the chlorination product (**76-2**) with O-benzyl glyoxal (**76-3**) and ammonia can be envisaged as proceeding thorough the aminal (**76-4**) of the glyoxal. Imine formation with dichloro reagent (**76-2**) by displacement of halogen then leads to imidazole (**76-5**). Reaction of that intermediate with iodine in a base leads to the iodo derivative (**76-6**). Displacement of iodine by the anion from 3-5-dichlorothiophenol (**76-7**) proceeds to give the thioether (**76-8**). The still-free imidazole nitrogen is next alkylated with 2-chloromethyl pyridine (**76-9**) to afford (**76-10**). The benzyl protecting group on oxygen is then removed by treatment with a strong acid. The thus-revealed carbinol in (**76-11**) is condensed with chorosulfonyl isocyanate to form the corresponding carbamate. There is thus obtained the NNRTI capravirine (**76-12**) [80].
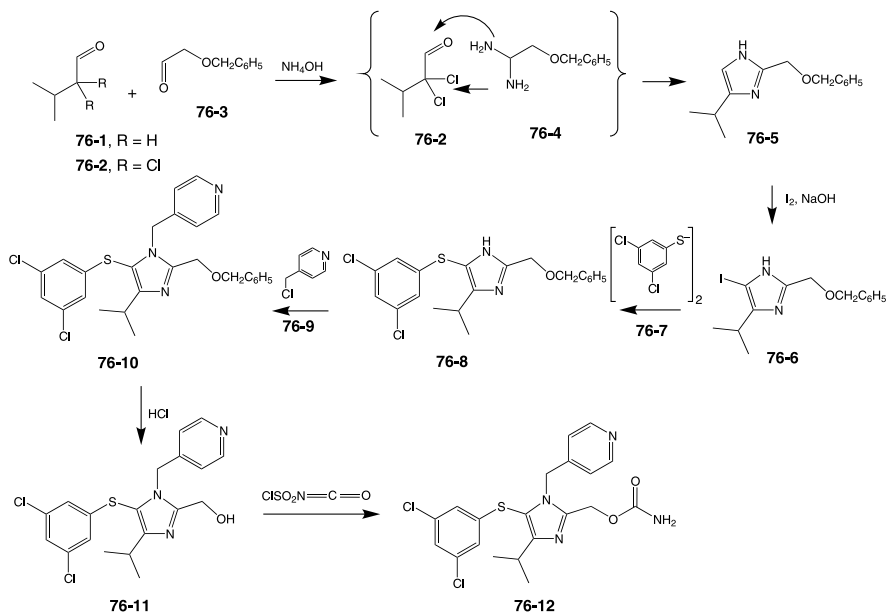
The role of angiotensin in hypertension and the development of the ACE inhibitors for treating elevated blood pressure were touched upon in some detail earlier. Compounds that inhibit the binding of angiotensin II at its receptor offer a more direct approach, avoiding rare possible effects from the inhibition of other peptidase targets. The finding in the 1970s that the peptide saralasin lowered elevated blood pressure by blocking angiotensin at its receptor site led to the search for nonpeptide receptor blockers. Three of the large groups of currently approved angiotensin receptor drugs share and imidazole moiety. Most of these compounds also incorporate a tetrazole as a surrogate carboxylic acid. The acidity of carboxylic acid is markedly enhanced by the fact that the negative charge in its anion can be dispersed over two atoms. Much the same holds true for a tetrazole devoid of nitrogen substituents, where the charge in the anion can be dispersed over all four nitrogens. The preparation of one of the first of these agents starts with the alkylation of the highly substitude imidazole (**77-1**) with the diphenylmethyl bromide (**77-2**) to afford the *N*-alkylated imidazole (**77-3**). A standard method for building tetrazoles, a ring sytem with a very acidic proton, comprises reaction of a nitrile with hydrazoic acid. Thus treatment of (**77-3**) with sodium azide and an acid converts the nitrile to a hydrazoic acid and thus **losartan** (**77-4**) [81].
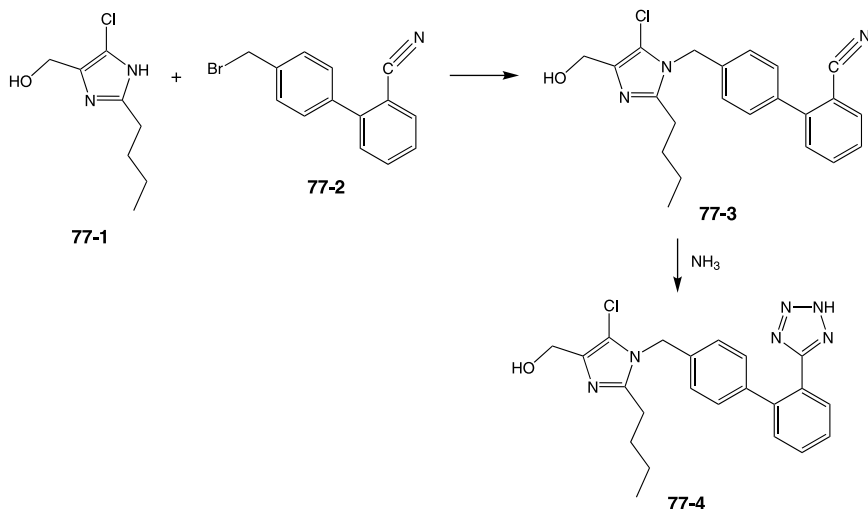
The seemingly complex imidazolone (**78-3**) is in fact obtained in a single step by reaction of the amino-ester (**78-1**) with the iminoether (**78-2**) derived from capronitrile. The relatively acidic proton on the heterocyclic ring is next removed by reaction with sodium hydride. This anion is then alkylated with the same biphenylmethyl bromide (**77-2**) that was used to prepare losartan to afford (**78-4**). The nitrile group is in this case converted to the tetrazole by means of tributyltin azide, a reagent that involves milder conditions than the traditional acidic medium used to generate hydrazoic acid. Thus, treatment of (**78-4**) with the tin reagent affords **irbesartan** (**75-5**) [82].
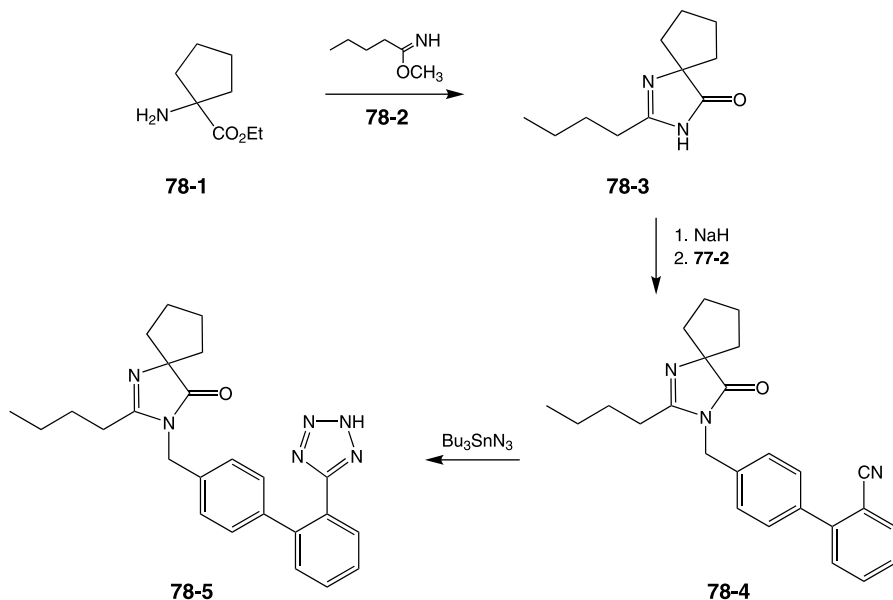
A benzofuran ring replaces one of the benzene rings of the biphenyl moiety present in many of the sartans in the rather more complex drug **saprisartan** (**80-10**). It is of note, further, that the acidic proton is provided in this case by a trifluorosulfonamide instead of the more common tetrazole ring. Construction of the imidazole fragment begins by nitrosation of the β-ketoester (**79-1**) by means of sodium nitrite in acid to afford the oxime (**79-2**). Reaction with acetyl chloride leads to the ester (**79-3**). Reaction of this last intermediate with the iminoether from propionitrile then affords the imidazole (**79-4**).
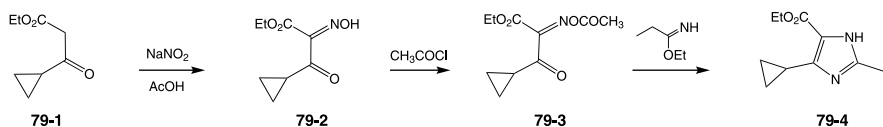
In the convergent scheme, palladium catalyzed coupling of the benzofuran boric acid (**80-1**) with ethyl 2-bromobenzoate (**80-2**) leads to the biphenyl surrogate (**80-3**). Sequential bromination and then saponification of that product then leads to the acid (**80-5**). Treatment of the acid with diphenylphosphinous azide in *tert*-butanol leads to a Curtius rearrangement of the acid to the corresponding isocyanate; that immediately reacts with solvent to afford the *tert*-butoxy carbamate (**80-6**). A second bromination, this time under more strenuos conditions, affords the bromomethyl intermediate (**80-7**). Reaction of this last with the imidazole (**79-4**) leads to the displacement of bromine and the formation of the alkylation product (**80-8**). The regiochemistry of the reaction may be rationalized by the predominance of the imidazole tautomer (**79-4**) due to chelation with the adjacent ester carbonyl. Treatment with trifluoroacetic acid leads to scission of the carbamate and the

formation of the aniline; reaction with trifluoromethylsulfonic anhydride then affords the necessary sulfonamide group (**80-9**). The acid formed on saponification of the ester on the imidazole is next activated by reaction with carbonyl di-imidazole. The imidaozide is then treated with ammonia to convert the carbonyl to an amide and thus afford saprisartan (**80-10**) [83].
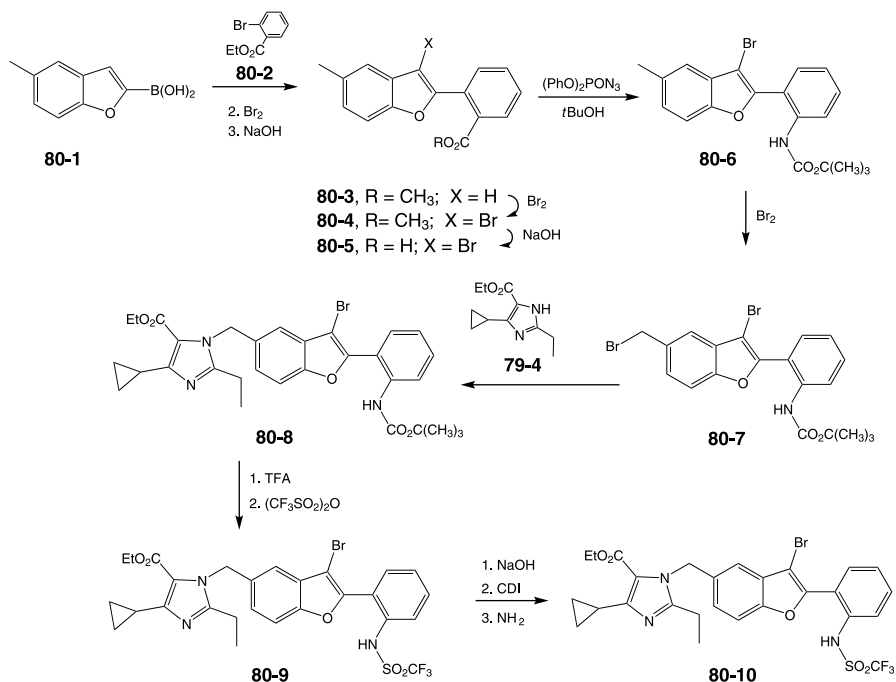
8.3.4. Imidazolines

Activation of α-adrenergic receptors, as a general rule, leads to the contraction of muscles in the innervated tissues. The net result of this action on the vasculature will be vasoconstriction and a consequent increase in blood pressure. Some of the first antihypertensive agents in fact consisted of imidazolines that blocked the response to endogenous α-adrenergic agonists; the extensive menu of side effects elicited by these drugs, possibly due to the fact that they blocked all α-receptor subtypes at other sites, led to their eventual replacement by more selective agents. Subtle structural differences lead to imidazolines that act as α-adrenergic agonists. Those are used to this day to induce vasoconstriction in peripheral tissue; they comprise the over-the-counter nasal decongestants and drops for treating eye irritations.

The schemes for preparing imidazolines take advantage of the fact that this heterocyclic system in effect consists simply of a cyclic amidine of ethylenediamine. Thus, treatment of the iminoether (**81-1**) from phenylacetonitrile with ethylenediamine can be envisaged to result in the initial displacement of ethoxide to give a transient intermediate such as (**81-2**); internal addition-elimination by the remaining side chain

amino group leads to the formation of the imidazoline ring. This leads in this case to the formation of the α-adrenergic blocker **tolazoline** (**81-3**) [84], a one-time vasodilator. The same sequence starting with the cyanotetralin (**81-4**) affords **tetra-hydrolozine** (**81-6**) [85]; this compound, in contrast to (**81-3**), is an α-agonist, used extensively as a vasoconstrictor for treating eye inflammation.
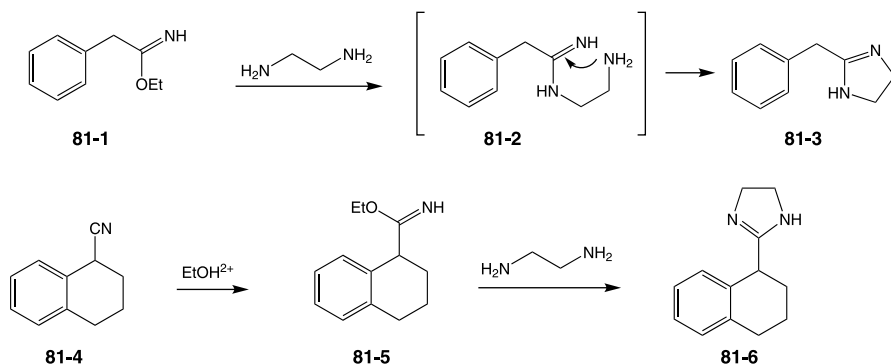
A very lipophilic, highly substituted benzene ring provides the side chain for the nasal decongestant α-blocker **xylometazoline** (**82-5**). The synthesis of this compound starts with the chloromethylation of the mesitylene derivative (**82-1**) followed by the displacement of chlorine by cyanide; there is thus obtained the arylacetonitrile (**82-3**). This is then converted to the corresponding imidazoline via iminoether (**82-4**) [86] by the sequence outlined above.
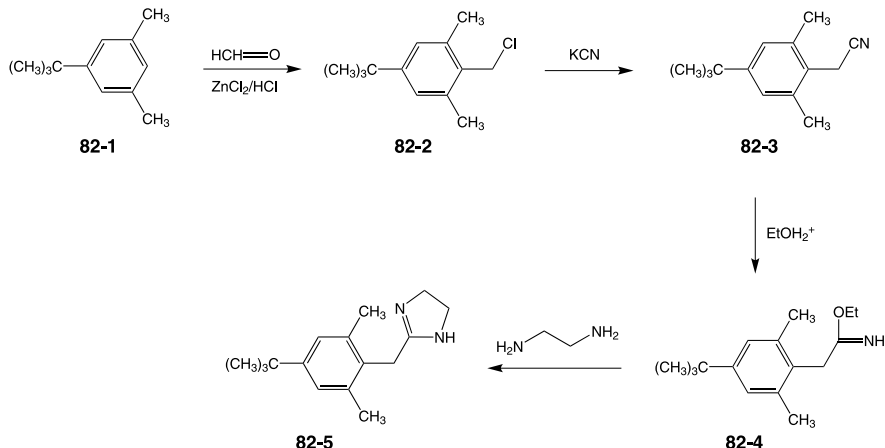
The α-blocker **phentolamine** (**83-3**) was used fairly extensively as an antihypertensive agent prior to the availability of more effective and far better tolerated drugs. Some of the most important side effects from use of this drug, such as fluid retention and tachycardia, were at that time attributed to compensatory mechanisms, casting a cloud on all α-blockers. The use of this class of agents for controlling elevated blood

pressure awaited the discovery of receptor subtype specific agents. One synthesis for this agent depends on the fact that the key intermediate (**83-2**) is in fact an α-amino-nitrile derivative of formaldehyde. The intermediate is thus obtained by reaction of the diarylamine (**83-1**) with formalin and potassium cyanide in the presence of mineral acid. The product from that reaction (**83-2**) is converted to **phentolamine** (**83-3**) by the usual sequence involving the reaction of the iminoether with ethylene diamine [87].
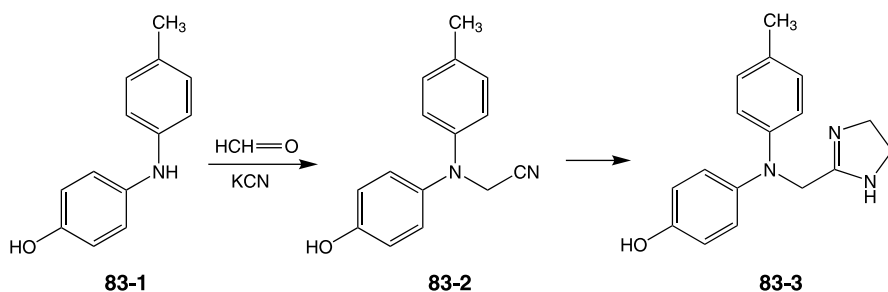
One approach aimed at developing structurally novel nasal decongestants involved the replacement of the methylene link present in most α-blockers by an amine [88]. Initial pharmacology on one of these analogues, **clonidine** (**84-4, 84-5**), indicated that the α-blocking activity had in fact been retained. The compound was, however, surprisingly found to be hypotensive in humans on oral administration. This activity was subsequently traced to the fact that the drug readily crosses the blood–brain barrier and the subsequent stimulation of α-adrenergic receptors in the brain resulted in the lowering of blood pressure. The drug soon found widespread use as an antihypertensive agent because of its good tolerability compared to the then-available alternatives. One of the early syntheses of this compound starts by formation of the methyl ether (**84-2**) from the cyclic thiocarbonate (**84-1**) from ethylene diamine by means of methyl
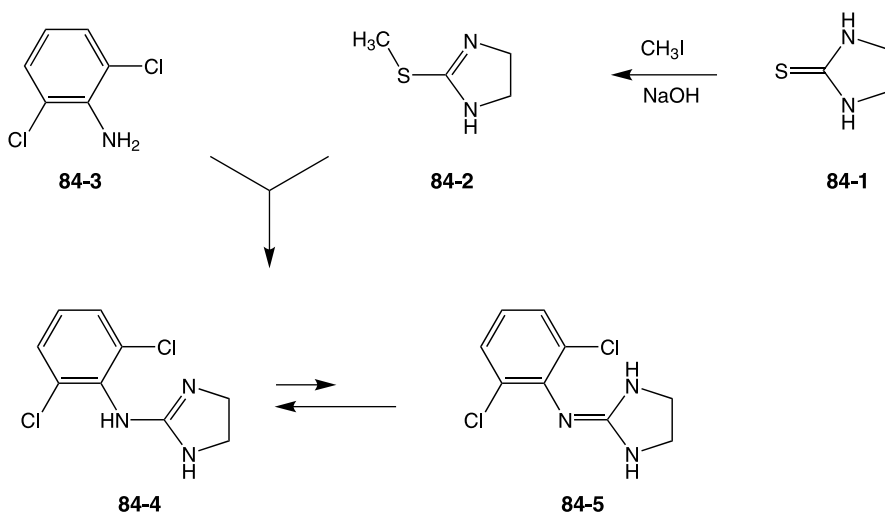
iodide and a base; this in essence converts the sulfur to a better (if odiferous) leaving group. Reaction of the thiomethyl ether with 2,6-disubstituted aniline (**84-3**) results in the displacement and formation of the cyclic guanidine; the *ortho* substituents are crucial for activity. There is thus obtained **clonidine** [89], shown as both the so-called "amino" tautomer (**84-4**) and its "imino" counterpart (**84-5**).

The frequently observed bioisosteric relation of benzene and thiophene applies to the **clonidine** series as well. Reaction of the thiophenyl thiourea (**85-1**), in which the amine group is flanked by substituents as in the prototype, with methyl iodide and a base gives the corresponding methyl thioether (**85-2**). Treatment of that inter-mediate with ethylene diamine leads to the formation of an imidazoline ring and the antihypertensive agent, **tiamenidine** (**85-3**) [90], shown as its "imino" tautomer.
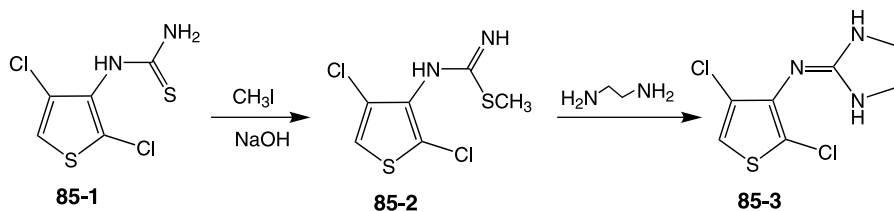
Antihypertensive agents, and α-blockers in particular, have been found to lower the intraocular pressure that marks glaucoma. The use of such drugs for treatment of this disease is limited by their propensity to lower blood pressure even in normo-tensive individuals. A sufficient amount of the drug is often absorbed even on topical application to make this a problem. Increasing the polarity of **clonidine** by addition of an amino group keeps the drug out of its locus of action in the brain while retaining its effect on intraocular pressure when applied locally. Nitration of **clonidine** intermedi-ate (**84-3**) leads to the nitroaniline (**86-1**). This is then converted to the corresponding formamide (**86-2**), for example, by ester interchange with ethyl formate. Treatment
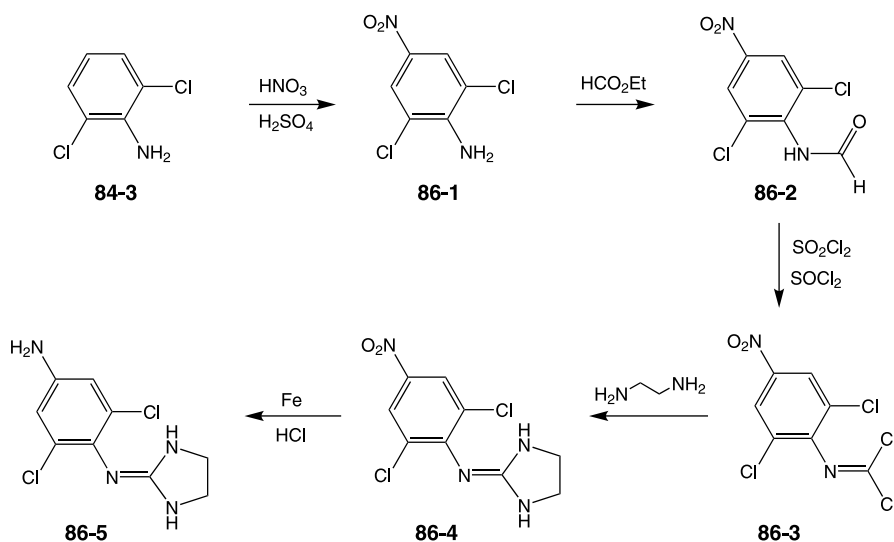
with a mixture of sulfuryl chloride and thionyl chloride results in the formation of the bischloroimino derivative (**86-3**). The halogens are then replaced by nitrogen by reaction of that intermediate with ethylene diamine to form the iminoimidazolidine (**86-4**) speculatively by sequential addition-elimination steps. Reduction of the nitro group with iron powder and hydrochloric acid then yields **apraclonidine** (**86-5**) [91].

8.3.5. Modified Imidazoles

A compound that includes a carbonyl group on the imidazoline ring is described as sedative. Treatment of the guanidyl substituted amino acid creatine (**87-1**) with hydrochloric acid results in cyclization to the iminoimidazolinone creatinine (**87-2**). Condensation of that intermediate with *meta*-chlorophenylisocyanate (**87-3**) leads to the formation of a urea by condensation of the reactive function with the imidazole as its amino tautomer. There is thus obtained **fenobam** (**87-4**) [92].
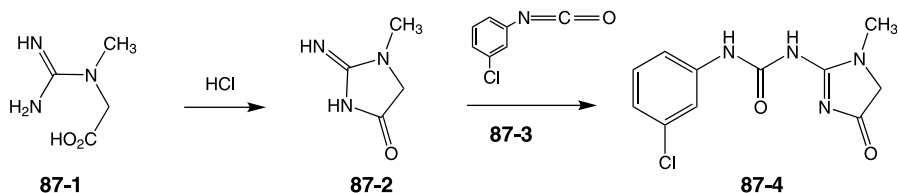
The apparently quite broad structural requirements for anticonvulsant activity, noted earlier in this chapter, extend to yet another class of five-membered hetero-cycles that include an imide function. Imidazo-2,4-diones, better known as hydan-toins, have comprised some of the most widely used drugs for treating severe motor and psychomotor epileptic seizures. The general reaction used to prepare this heterocyclic system involves the treatment of a carbonyl compound with ammonium carbonate and potassium cyanide. The first step in the complex sequence can be visualized as the addition of the elements of ammonia and hydrogen cyanide to give an α-aminonitrile (**88-2**). Addition of ammonia to the cyano group would then lead to an amidine (**88-3**). Carbon dioxide or carbonate ion present in the reaction
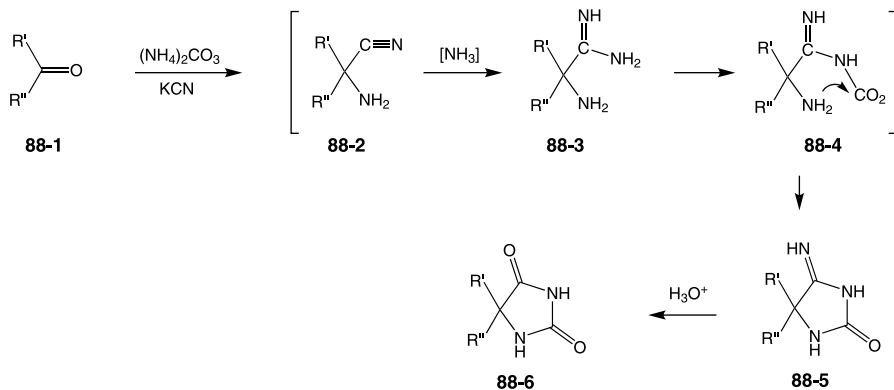
mixture can then add to the quite basic amidine to afford a carbamic acid such as the intermediate (**88-4**); attack by the adjacent amino group will then close the ring and afford the isolable imino derivative (**88-5**). This is then hydrolyzed to a hydantoin (**88-6**) by treatment with aqueous acid.

Alkylation of the hydantoin (**89-2**) from benzaldehyde with ethyl iodide takes place at the imide nitrogen to afford **ethitoin** (**89-3**) [93]. In much the same vein, treatment of the hydantoin (**89-5**) from propiophenone with methyl iodide (**89-5**) in the presence of a base affords **mephenytoin** (**89-6**) [94]. Replacement of the quite acidic imide proton by an alkyl group is not required for activity; the well-known anticonvulsant **phenytoin** (**89-8**) consists of simply the hydantoin obtained from benzophenone (**89-7**) [95]; this is often formulated as its sodium salt.

89-1, R = H

89-4, R = C₂H5

89-7, R = C₆H₅

89-2, R = H

89-5, R = C₂H₅

89-8, R = C₆H₅

89-3, R = H; R' = C₂H₅

89-6, R = C₂H₅; R' = CH₃
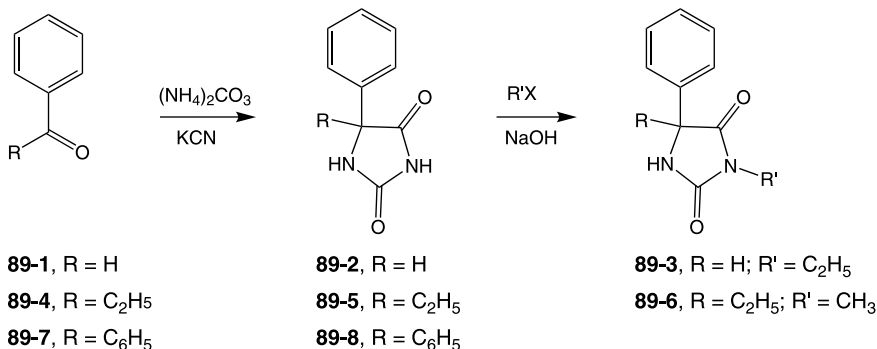
The use of phenitoin in the clinic is complicated by the great variation in blood levels observed on oral administration of the drug, particularly in those cases where those levels need to be closely adjusted. A water-soluble derivative that allows the drug to be administered parenterally permits more accurate adjustment of blood levels as well as treating patients on the threshold of consciousness. The derivative is converted back to the parent drug in the circulation. The preparation

89-8

90-1

90-2

90-4

90-3
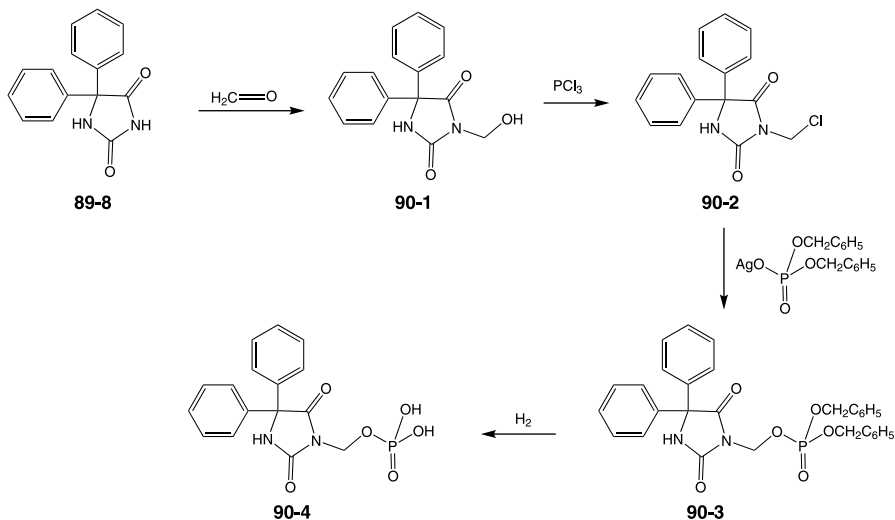
of this derivative **fosphenitoin** (**90-4**) starts by conversion of phenitoin itself (**89-8**) by reaction with formaldehyde. Treatment of the intermediate (**90-1**) with phosphorus trichloride replaces the hydroxyl group by chlorine (**90-2**). Displacement of halogen by silver dibenzylphosphate leads to the protected phosphate ester (**90-3**). Hydrogenolysis then removes the benzyl protecting groups to afford the free acid and thus fosphenitoin (**90-4**) [96].

A somewhat different scheme is used for the preparation of an all-aliphatic thiohydantoin. Thus, reaction of racemic leucine (**91-1**) with allylisothiocyanate (**91-2**) leads to the thiourea (**91-3**). Attack of the anion from treatment of that intermediate with a strong base leads to ring closure and the formation of the imidazoline ring. There is thus obtained the anticonvulsant agent **albutoin** (**91-4**) [97].
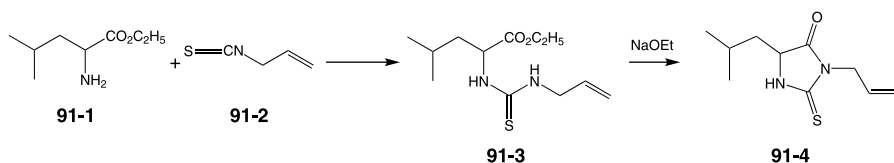
The preparation of a pair of iminohydantoins invokes the addition of amide nitrogen to a cyano group for formation of the imidazole ring. The products exhibit unexpectedly quite different biological activities. Reaction of the cyanamide (**92-1**) from *para*-chloroaniline and cyanogen bromide with *N*-methylchloroacetamide (**92-2**) can be visualized to lead initially to the alkylation product (**92-3**). Cyclization by addition to the nitrile group then affords **clazolamine** (**92-4**) [98], a compound described as a diuretic.
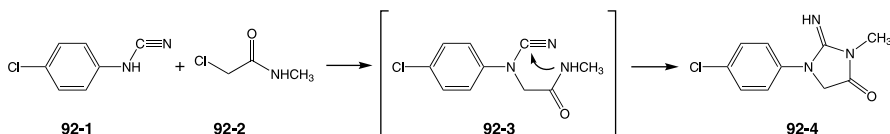
In a similar vein, reaction of *bis*-cyanoethylamine (**93-2**) with *para*-chlorophenylisocyanate (**93-1**) gives the urea addition product (**93-3**), in this case as an isolable product. Heating that compound leads to an analogous addition reaction to form the imidazole ring. The product **nimazone** (**93-4**) [99] displays antiinflamatory activity.
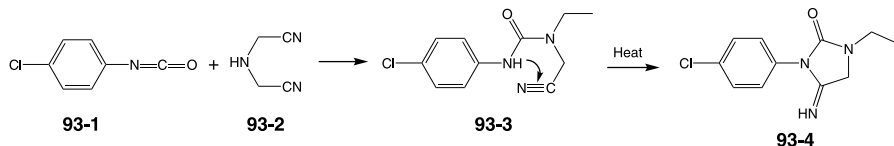
One of the grave sequelia of rheumatoid arthritis involves the destruction of cartilage catalyzed by collagenase enzymes. Considerable work has, as a result, been devoted to uncovering inhibitors of that enzyme. A hydantoin forms a central moiety of the inhibitor **cipemastat** (**94-12**). The first step in the convergent synthesis starts by protection of the chiral hydroxyl acid (**94-1**) as its benzyl ester (**94-2**). The

hydroxyl group is then activated toward displacement by conversion to its triflate (**94-3**) by reaction with trifluoromethane sulfonate. Reaction of that with the anion from the unsymmetrical malonate ester leads to a triester (**94-4**) in which the configuration about the chiral center has been inverted.

The α-aminonitrile (**94-5**) from acetone and methylamine comprises a starting material for the heterocyclic ring. Reaction of that compound with chlorosulfonyl isocyanate and hydrochloric acid gives hydantoin (**94-6**). In a sequence similar to that used above for fosphenitoin, treatment of that heterocycle with formaldehyde leads to a carbinol from addition to the free amino group on the imidazole-dione. The hydroxyl group is then converted to the bromo derivative (**94-7**) with phosphorus tribromide [100]. Use of this intermediate to alkylate the enolate from (**94-4**) gives (**94-8**). Catalytic hydrogenation of this product leads to the formation of the corresponding ester-diacid by loss of the benzyl protection groups on two of the esters. Heating this last intermediate in the presence of *N*-methylmorpholine causes the free acid on the carbon bearing the *tert*-butyl ester to decarboxylate (**94-9**). The desired stereoisomer (**94-9**) predominates, in effect reflecting the selectivity of the alkylation step (**94-4** → **94-8**) caused by the presence of the preexisting adjacent chiral center. The free carboxylic acid group is then condensed with piperidine to form amide (**94-10**). The remaining ester is then hydrolyzed in acid to afford the acid (**94-11**). Reaction of this last with *O*-benzylhydroxylamine followed by hydrogenolysis of the benzyl group then leads to the hydroxamic acid and thus the collagenase inhibitor cipemastat (**94-12**) [101].
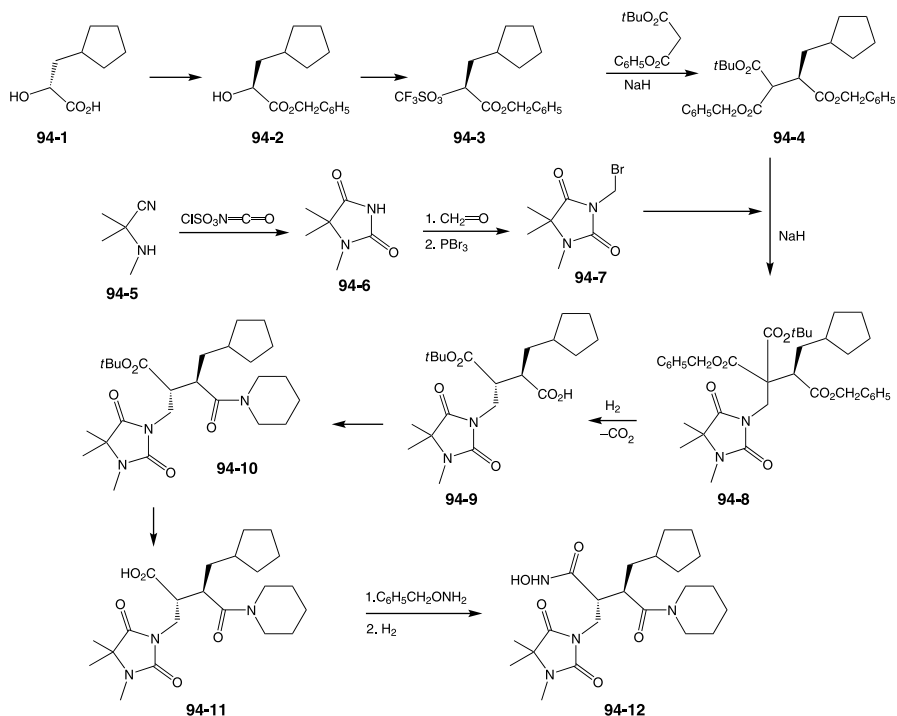
The hydroxylation of dopamine in sympathetic nerves to form the pressor neurotransmiter epinephrine is catalyzed by the enzyme dopamine-β-hydroxylase. Antagonism of the enzyme would be expected to diminish the production of that neurotransmitter and as a consequence lower blood pressure. This would achieve an effect on the cardiovascular system more directly than either α- or β-blockers. The synthesis of the specific hydroxylase inhibitor **nepicastat** (**95-11**) starts by reaction of aspartic acid (**95-1**) with trifluoroactetic anhydride. This reagent results in the conversion of the amine to its trifloroacetamide derivative and the acid to an anhydride (**95-2**). Reaction of this intermediate with 1,3-difluorobenzene in the presence of aluminum chloride gives the Friedel–Crafts acylation product (**95-3**). Catalytic hydrogenation then reduces the ketone to a methylene group (**95-4**). A second acylation reaction, this time via the acid chloride, results in an intramolecular reaction to form the tetralone (**95-5**). The new carbonyl group is again reduced by means of hydrogenation; saponification then removes the protecting trifluoroacyl group to give the primary amine (**95-6**) as a single enantiomer. Reaction of that amine with formaldehyde and potasium cyanide leads to the formation of what is essentially an α-aminonitrile (**95-7**), the nitrogen analogue of a cyanohydrin. The amino group is then taken on to a formamide by reaction with butyl formate (**95-8**). Formylation of the carbon adjacent to the nitrile by means of ethyl formate and sodium ethoxide puts into place the last carbon for the imidazole ring (**95-9**). Reaction of this last product as its enolate with thiocyanate forms the cyclic thiourea (**95-10**). Catalytic hydrogenation then serves to reduce the nitrile to the corresponding amino-methylene derivative and thus nepicastat (**95-11**) [102].
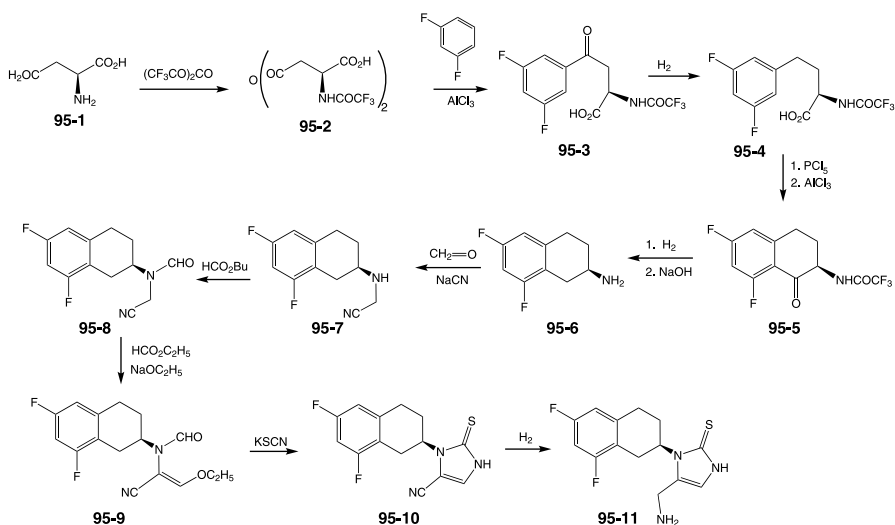
8.3.6. Pyrrazolones and Pyrrazolodiones

Some of the first therapeutic agents that showed documented activity in humans consisted of substituted pyrrazoles. The pyrrazolone-based antipyretic and

antiinflamatory agent antipyrine (**96-2**) first came into use at about the same time as aspirin. The large number of side effects due to the use of this drug and some of its analogues led to their eventual abandonment. They are discussed here for the illustrative value of their chemistry. It is of note that these compounds do not possess an acidic center, unlike the prrazolodiones that follow. The parent pyrrazolone (**96-1**) is obtainable in a straightforward fashion from the reaction of ethyl acetoacetate with phenylhydrazine; the regiochemistry is dictated by the formation of an enamide by reaction of the acetoacetate enol with the more basic and less substituted hydrazine amino group; ester-amine interchange involving the anilide nitrogen then leads to ring formation. Alkylation of the intermediate with methyl iodide completes the preparation of **antipyrine** (**96-2**). Reaction of that compound with nitrous acid interestingly leads to a reaction on the heterocycle rather than on the benzene ring forming the nitroso derivative (**96-3**). Reduction of the newly introduced function gives the at one time widely used anti-inflamatory drug **aminopyrine** (**96-4**). Alkylation with isopropyl bromide gives **isopyrine** (**96-5**) [103], while acylation with nicotinoyl chloride (**96-6**) affords **nifemazone** (**96-7**) [104].
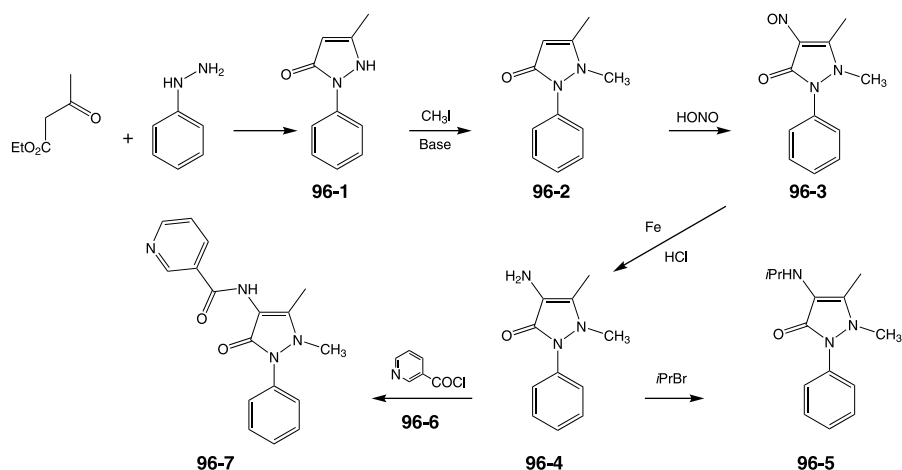
The diarylpyrrazolodione class of antiinflamatory agents is of more recent origin, having been developed from the late 1950s on. Only representative examples are discussed below because this class also fell into disuse as a result of toxicity problems. The first and most widely used drug from this class is **phenylbutazone** (**97-5**). This compound, which in effect is a double lactam of *sym*-diphenylhydrazine (**97-3**), can be prepared by reaction of the latter with diethyl propylmalonate (**97-4**) in the presence of a base [105]; this compound, it should be noted, incorporates the acidic proton that marks the classic heterocyclic NSAIDs as well as the two aryl groups that characterize the much more recent COX-2 specific drugs.

Detailed pharmacokinetic studies on **phenylbutazone** revealed that the principal metabolite consists of a phenol from the hydroxylation of one of the aromatic rings (**97-8**). The finding that this compound was more potent than the parent drug led to its introduction as a drug in its own right. Coupling of the benzenediazonium

chloride (**97-1**) with phenol gives the corresponding azo derivative (**97-2**); the free hydroxyl is then protected as a benzyl ether (**97-6**) by reaction of the phenoxide with benzyl bromide. Condensation of this with diethyl butylmalonate leads to the pyrazolodione (**97-7**). Removal of the protecting group by hydrogenolysis over palladium affords the NSAID **oxyphenbutazone** (**97-8**) [106].

The addition of a phenylsulfoxide moiety to the end of the side chain markedly changes the activity of this class of compounds. This product, **sulfinpyrazone** (**97-11**), stimulates uric acid excretion, making it a valuable drug for dealing with the elevated serum uric acid levels associated with gout. The compound is still one of the more important uricosuric agents available today. The starting ester (**96-9**) is available by alkylation of the dianion from ethyl malonate with 2-chloroethylphenyl thioether. Condensation with diphenylhydrazine (**97-3**) in the presence of a base then affords the pyrazolodione (**97-10**). Oxidation of sulfur with a controlled amount of hydrogen peroxide leads to the sulfoxide and thus **sulfinpyrazone** (**97-11**) [107].
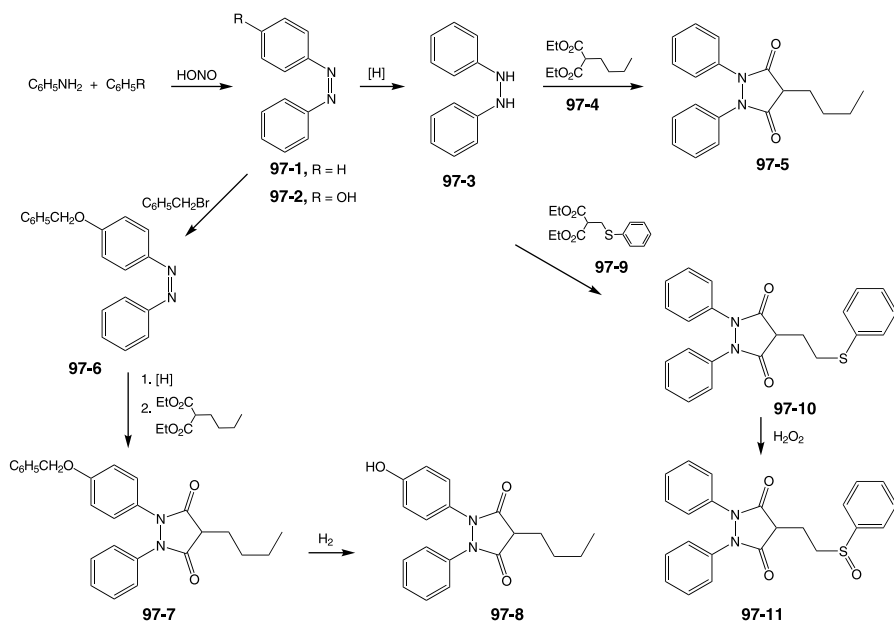
The discovery of canabinol receptors has led to the search for synthetic agonists and antagonists based on structures that differ significantly from those of the hemp-related products. One of the first antagonists to come out of those programs, **rimonabant** (**98-6**), has shown activity as an appetite-suppressant weight loss agent. Reaction of the anion from propiophenone (**98-1**) with ethyl oxalate gives the enolate (**98-2**). Condensation of that with 2,4-dichlorophenylhydrazine (**98-3**) results in the formation of imines between carbonyl groups and the basic nitrogen, thus forming the pyrazole ring (**98-4**). The side chain ester is then saponified to afford the corresponding acid (**98-5**). This is then reacted with *N*-aminopiperidine in the presence of DCC to form the amide rimonabant (**98-6**) [108].
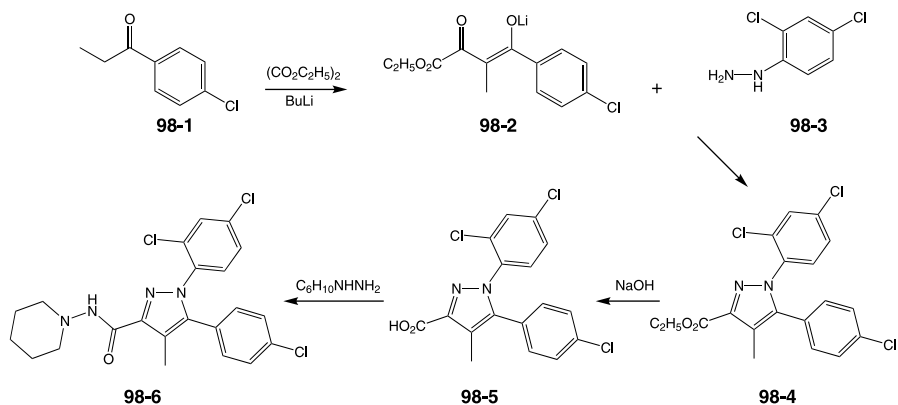
8.3.7. Thiazoles and Related Sulfur–Nitrogen-Containing Heterocycles

The very broad structural requirements for NSAIDs that allow replacement of the benzene ring by a pyrrole or an oxazole ring have been noted earlier in this chapter. Thiazoles, too, it has been found, can substitute for the central benzene ring.

One of the two classic schemes for constructing the thiazole ring involves the condensation of a thioamide or its equivalent with an α-haloketone. The reaction can be visualized as involving, as the first step, the displacement of halogen by sulfur from the enol form of the amide; imine formation will then close the ring. Thus, reaction of bromoketone (**99-2**) obtained from the bromination of the corresponding keto-acid with thioamide (**99-1**) affords thiazole (**99-3**) in a single step. There is thus obtained the NSAID **fentiazac** [109].
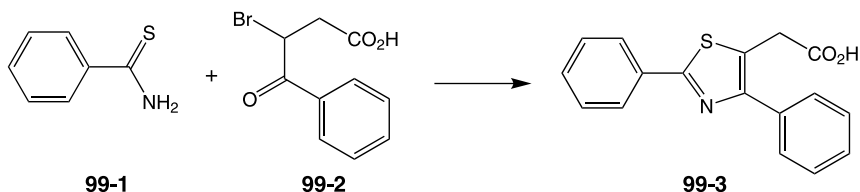
In a similar vein, reaction of the thiobenzamide (**100-1**) with 4-bromoacetoacetate (**100-2**) in the presence of a base starts by the displacement of bromine by sulfur to afford a transitory substitution product such as (**100-3**). This can then undergo internal imine formation between basic nitrogen and the adjacent carbonyl goup to afford the thiazole (**100-4**). Saponification then leads to the NSAID **fenclosic acid** (**100-5**) [110].
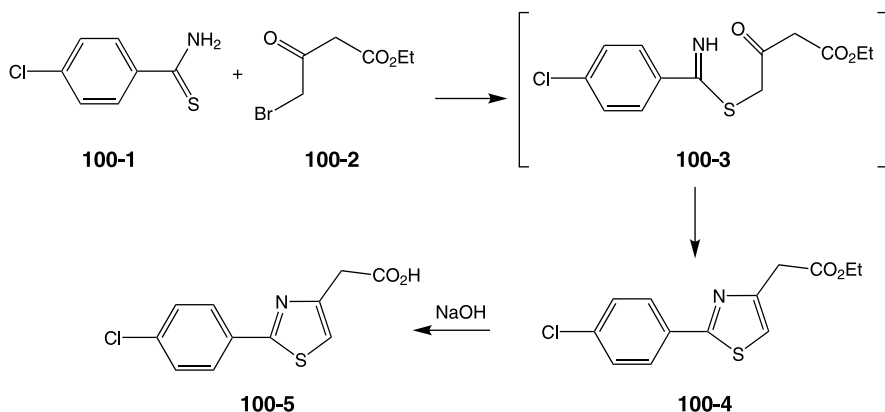
As noted previously, the 3,4-dianisylthiazole **itazigrel** (**101-3**) can in some ways be considered the founding lead for what became the series of COX-2 inhibitory NSAIDS. Since the synthesis of the compound preceded the finding of the existence of COX subtypes, it was investigated largely as an inhibitor of platelet aggregation. It is of interest to note in passing that an earlier analogue in which the trifluoromethyl group is replaced by methyl shows very similar activity [111]. **Itazigrel** (**101-3**) is obtained in a straightforward fashion by condensation of trifluoroacetamide (**101-1**) with bromodesoxyanisoin (**101-2**) [112].
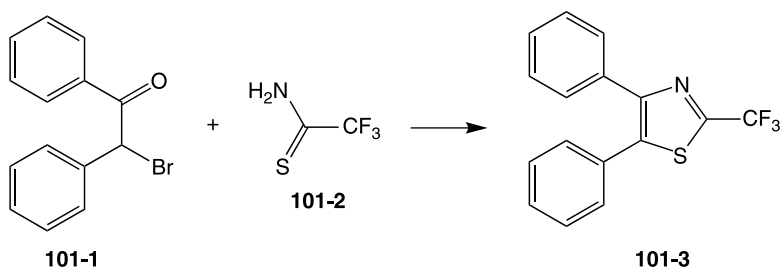
A 1,2,5-thiadiazole ring replaces the benzene ring that provides the nucleus found in most β-blockers in the widely used agent **timolol** (**124-8**), which is discussed later in this chapter. The simpler analogue based on a thiazole ring also acts as a β-adrenergic blocker. The first step consists in the displacement of the enol bromide-like halogen in bromothialzole (**102-1**) with the alkoxide from racemic glycerol acetonide
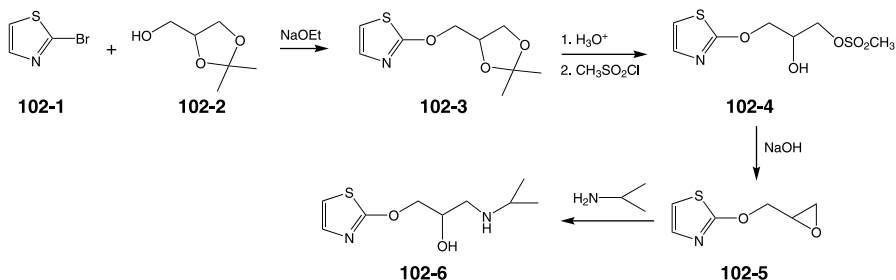
(**102-2**) to give the ether (**102-3**). The diol obtained on hydrolysis of the acetonide function is then converted preferentially to the mesylate (**102-4**) from the primary alcohol by reaction with methanesulfonyl chloride. The mesylate is then converted to the aminoalcohol by the standard β-blocker sequence: Conversion to the epoxide (**102-5**) with sodium hydroxide, followed by ring opening with isopropylamine. There is thus obtained **tazolol** (**102-6**) [113].

Thioureas serve as a convenient starting material for 2-aminothiazoles. Reaction of β-phenethylamine (**103-1**) with ammonium isothiocyanate gives the thiourea (**103-2**). Treatment of that product with phenacyl bromide (**103-3**) leads to the corresponding thiazole. That compound, **fanetizole** (**102-4**) [114], shows immunoregulating activity.
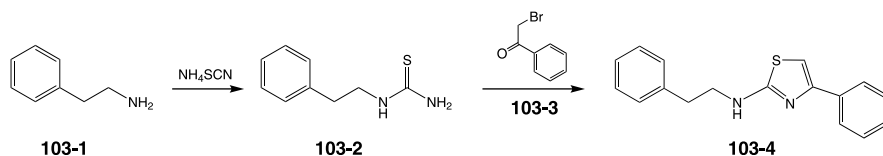
The interchangeabilty of five-membered heterocyclic rings extends to histamine H_2 blockers as well. Replacement of the imidazole in cimetidine by furan to give ranitidine includes some additional changes in functionality. The furan ring in the latter can, however, be replaced directly by thiazole. The starting thiazole (**104-3**) is prepared by the standard route of condensation of thioamide (**104-1**) with ethyl bromoacetate (**104-2**). Reduction of the ester group in (**104-3**) by means of lithium aluminum hydride leads to the corresponding methyl carbinol; this is then converted to the bromide (**104-4**). The displacement of bromine by cysteamine incorporates the required side chain (**104-5**). A reagent (**104-6**) can be prepared by a reaction of the ranitidine *bis*-methylthio nitrovinyl intermediate with methylamine. Treatment of the primary amine (**104-5**) with (**104-6**) leads to an addition of the nitrovinyl group and the formation of **nizatidine** (**104-7**) [115].
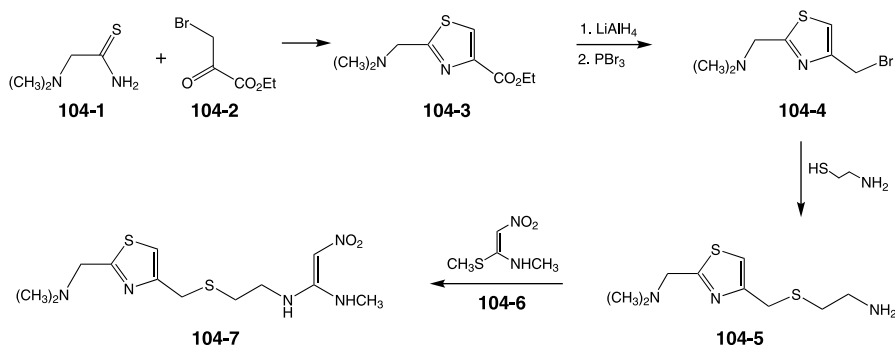
The addition of a mercaptide to a nitrile provides the key reaction to the preparation of a thiazolidinone that shows diuretic activity. The first step in the reaction of ethyl 2-mercaptoacetate (**105-2**) with ethyl cyanoacetate (**105-1**) thus probably leads first to the formation of the addition product (**105-3**). The imino

group, or its precursor anion, then attacks the adjacent ester to form a lactam and thus the thiazolidinone (**105-4**). Reaction of this intermediate with a base apparently results in an ambient anion that alkylates on nitrogen on treatment with methyl iodide to afford the product with the exocyclic olefin (**105-5**) as a single isomer. Bromination proceeds at the position adjacent to the carbonyl group to give (**105-6**). The displacement of halogen with piperidine then gives **ozolinone** (**105-7**) [116].
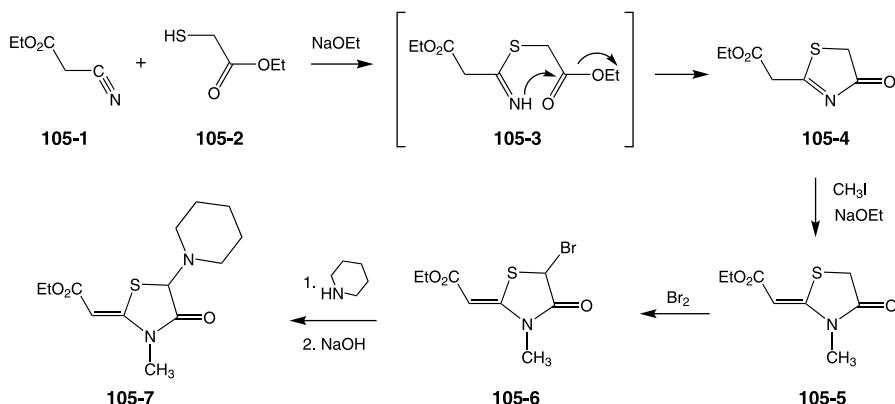
The sulfonylurea drugs used to treat Type II diabetes, covered in Chapter 2, work largely by stimulating the release of insulin from pancreatic beta cells. The "glitazones" comprise a series of antidiabetic compounds that share a thiazolidenedione that was first introduced about a decade ago. These drugs interact with gamma peroxisome proliferator–activated receptors (PPAR), a transcription factor that regulates the expression of specific genes involved in cell metabolism. The overall effect is expressed as an increased sensitivity to insulin.

The first step in the construction of the terminal side chain in the first glitazones comprises a reaction of benzaldehyde (**106-1**) with the mono-oxime (**106-2**) from biacetyl to afford the benzoxazole *N*-oxide (**106-3**). Reaction of that intermediate with phosphorus oxychloride leads the chlorination of the adjacent methyl group in a version of the Plonovski reaction to afford the choromethyl derivative (**106-4**). This is then used to alkylate the carbanion from the substituted acetoacetate
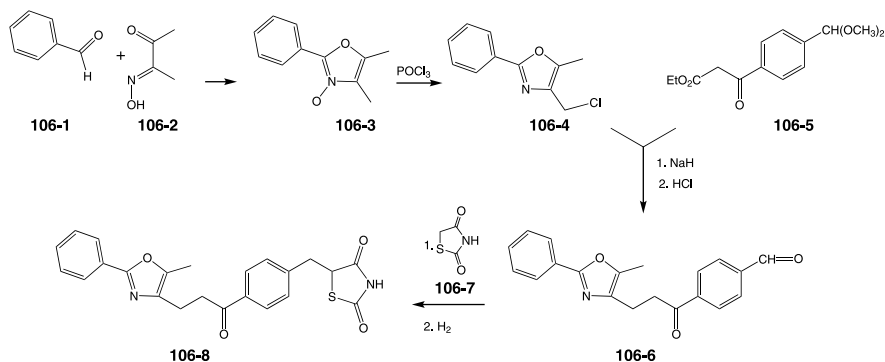
(**106-5**). Heating the first-obtained product in a strong acid leads to the hydrolysis of the ester. The resulting β-ketoacid loses carbon dioxide under reaction conditions; the acetal hydrolyses also reveal the free aldehyde (**106-6**). Aldol condensation of this last intermediate in the presence of a base with readily available rhodanine (**106-7**) links the two fragments. The double bond in the first-formed product is then reduced catalytically to afford **darglitazone** (**106-8**) [117].

The synthesis of the first of a pair of glitazones is based on chromans and starts by the protection of the phenol in chromancarboxylic acid (**107-1**) as its methoxy-methylene derivative by alkylation with methoxymethylene chloride. Reaction of that intermediate with lithium aluminum hydride reduces the ester to the corre-sponding carbinol (**107-2**). The nuleophilic aromatic displacement of chlorine in 4-chloronitrobenzene (**107-3**) by the alkoxide from (**107-2**) leads to the coupling product (**107-4**). Catalytic hydrogenation then reduces the nitro group to an aniline (**107-5**). The newly formed amine is then treated with nitrous acid to afford a diazonium salt. This reactive intermediate is then allowed to react with ethyl acrylate. This leads to the addition of the aromatic cation to the acrylate by the relatively little-known Meerwein reaction; chloride ion from the salt adds to the carbocation at the adjacent position to afford α-chloro-ester (**107-6**). The ester grouping is next saponified to the corresponding free acid; the acetate is cleaved under reaction conditions to afford (**107-7**). Reaction of the chloro acid function with thiourea proceeds to form a thiazolidinedione in a manner analogous to the formation of thiazole from haloketones. There is thus obtained **troglitazone** (**107-8**) [118].
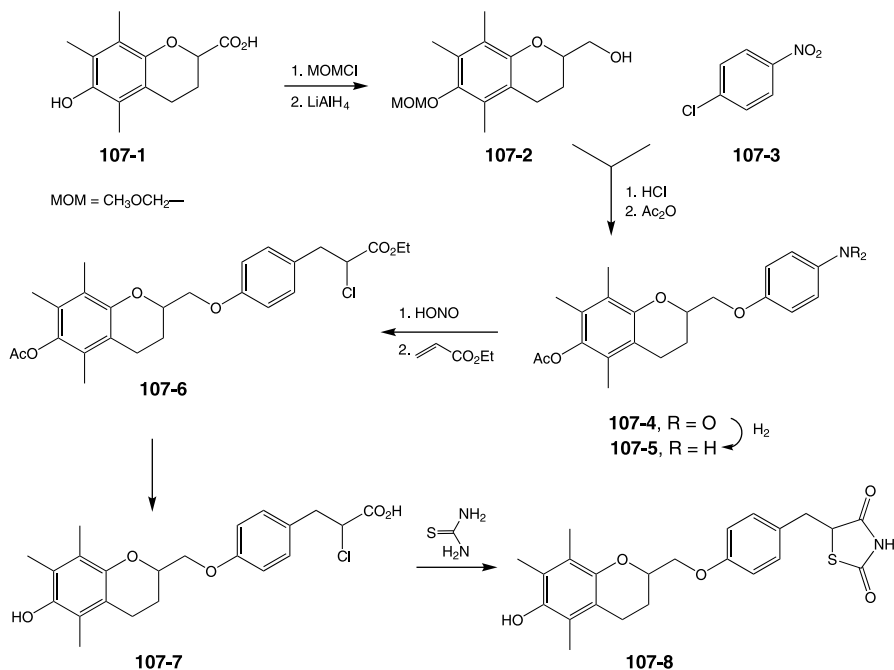
The reaction of chroman (**108-1**) with benzylmagnesium bromide probably takes place by way of the small portion of that acetal that equilibrates with the open form (**108-2**). Treatment of the crude diol (**108-3**) with *p*-toluenesulfonic acid (TSA) leads to the cyclodehydration product, chroman (**108-4**). The bromine on the aromatic ring is then changed to a lithio reagent by reaction with butyl lithium. Treatment of this organometallic reagent with carbon dioxide then affords the carboxylic acid (**108-5**). That product is next resolved by salt formation with a chiral amine. The carboxylic acid in the desired isomer is then reduced to an aldehyde. Condensation of that carbonyl group with rhodanine in the presence of the surprisingly mild base sodium hydroxide introduces the necessary thiazolidenedione moiety (**108-7**). Reduction of the newly introduced olefin completes the synthesis of **englitazone** (**108-8**) [119].
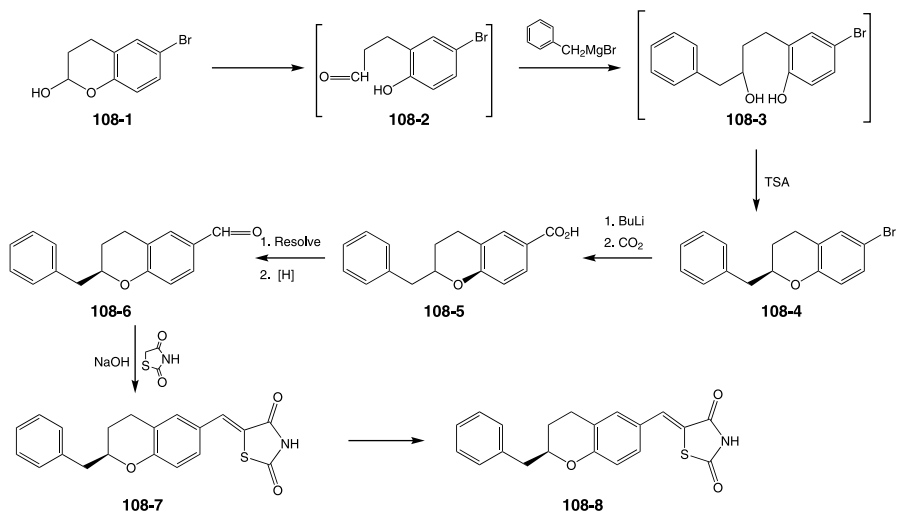
The synthesis of yet another drug candidate in this group begins with the reduction of the carboxylic acid in the naphthol (**109-1**) with diborane. The resulting carbinol is oxidized back to an aldehyde (**109-2**) by means of manganese dioxide. Aldol-type condensation of that with the active methylene group in rhodanine itself leads to the unsaturated intermediate (**109-3**). Catalytic hydrogenation next serves to reduce the double bond (**109-4**). The free phenol in the other ring is then alkylated with ortho-fluorobenzyl chloride (**109-5**) in the presence of a base. There is thus obtained the hypoglycemic agent **netoglitazone** (**109-6**) [120].
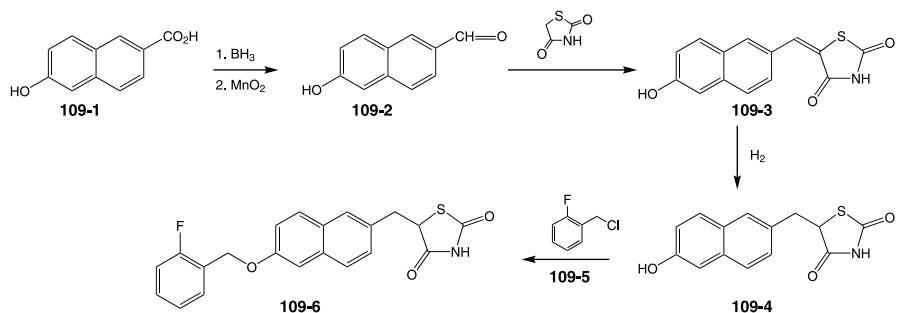
The enzyme xanthine oxidase mediates the metabolic disposition of xanthine and hypoxathine that results in the formation of uric acid. The pathology of gout is due in great part to an accumulation of this metabolite. One of the earliest drugs for treating gout is allopurinol (see Chapter14), which inhibits the accumulation of uric acid by inhibiting xanthine oxidase. One of the rare isothiazoles that has received a generic name, **amflutizole** (**110-5**), shares this activity. The key intermediate for the synthesis of this compound consists of the toluenesulfonyl derivative (**110-1**) of the oxime of the acid cyanide of *meta*-trifluromethylbenzoic acid. Reaction with ethyl 2-mercaptoacetate in the presence of a base results in the displacement of the tosylate by mercaptide and the formation of the N—S bond. This is then converted to the carbanion (**110-2**) by a second equivalent of base. This adds to the cyano group; protonation then goes on to form the imine (**110-3**), which tautomerizes to the amino form (**110-4**). Saponification of the ester then affords **amflutizole** (**110-5**) [121].
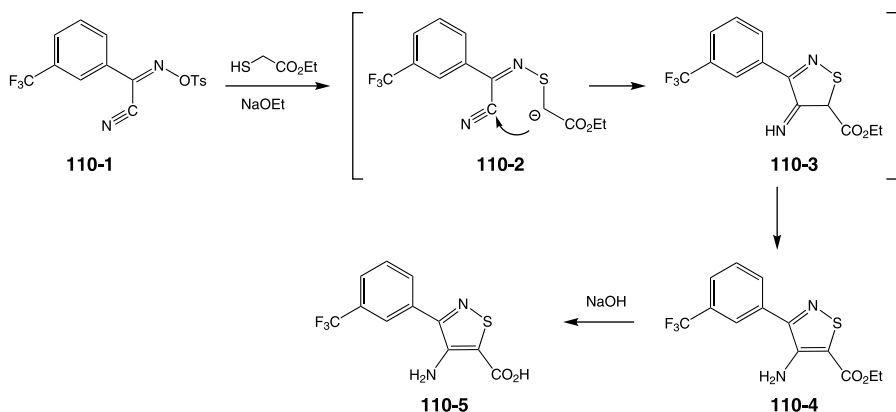
8.4. RINGS THAT CONTAIN THREE OR MORE HETEROATOMS

8.4.1. 1,2,4-Oxadiazoles

The syntheses of the 1,2,4-oxadiazole systems described below all rely on hydroxylamine for providing a preformed N-O linkage. The preparation of the respiratory anti-inflamatory and antitussive agent, **oxolamine** (**111-4**), starts by acylation of the alkoxide from the *N*-hydroxyamidine (**111-1**) with 3-chloropropionyl chloride; the presence of the negative charge on oxygen results in the formation of the *O*-acylated product (**111-2**). Treatment of that intermediate with triethylamine leads to cyclization via imine formation to afford the 1,2,4-oxadiazole (**111-3**). Displacement of the terminal chlorine with diethylamine gives the corresponding amine **oxolamine** (**111-4**) [122].
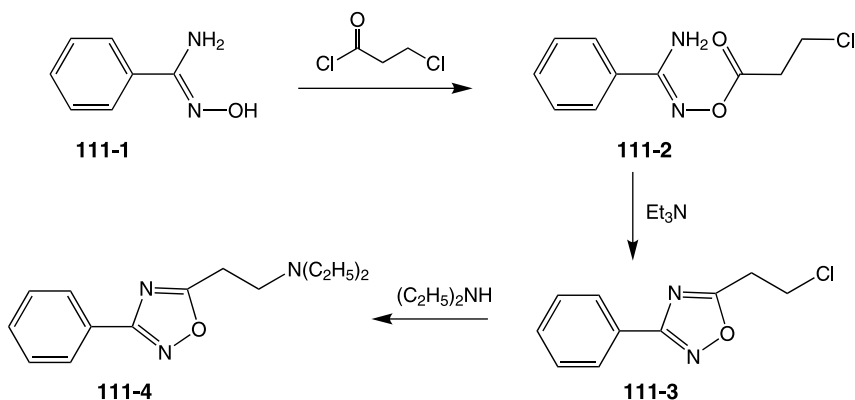
Acylation of *N*-hydroxy-2-phenylbutyramidine (**112-1**) with 3-chloropropionyl chloride in the absence of an added base proceeds as might be expected to give the product (**112-2**) from acylation on the more basic nitrogen. Heating this compound leads to the formation of the oxadiazole (**112-3**) almost certainly via the enol tautomer of the amide. Displacement of the terminal chlorine with diethylamine leads to the tertiary amine and thus **proxazole** (**112-4**) [123], a compound that is said to exhibit antispasmodic activity.
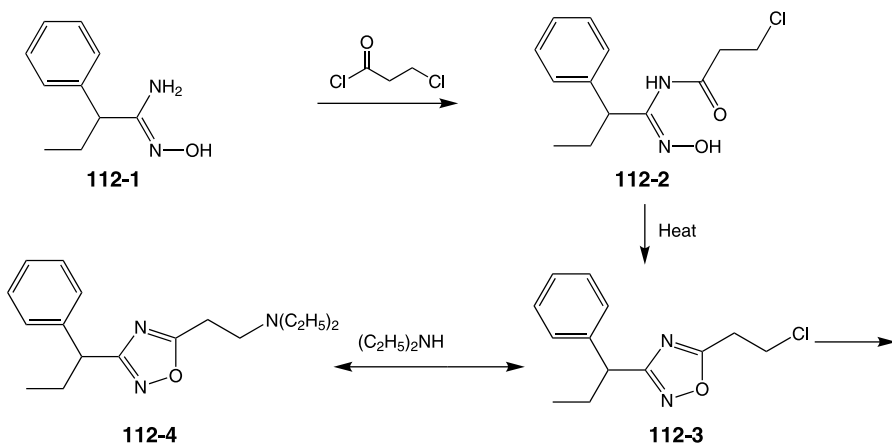
Reaction of the urea (**113-1**) derived from the hydroxyamidine (**111-1**) with phosphorus oxychloride represents an alternative method for forming the oxadiazole ring. The first step in the sequence can be visualized as a formation of the imino chloride (**113-2**). Internal displacement by oxime oxygen then gives the cyclization product (**113-3**), which is in tautomeric equilibrium with the imino form (**113-4**). Alkylation with 2-chlorotriethylamine interestingly proceeds via the latter unconjugated tautomer. There is thus obtained **imolamine** (**113-5**) [124], a compound that has been described as an antianginal agent.
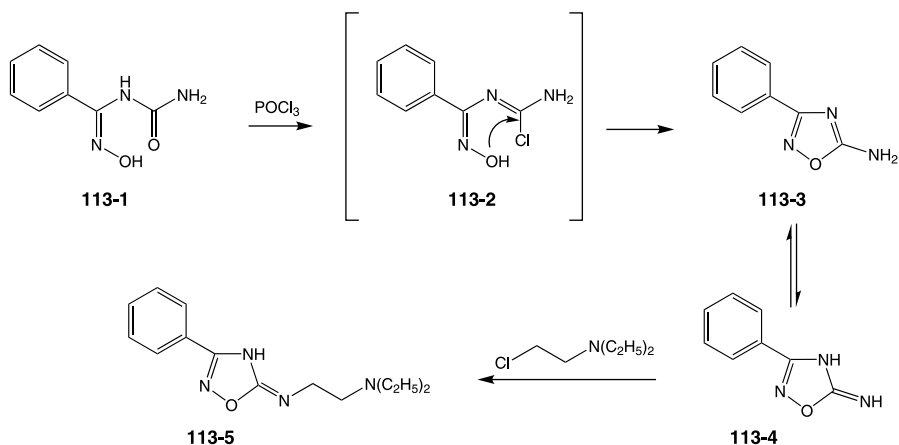
8.4.2. Triazoles

The great majority of "conazole" antifungal agents discussed above share an *N*-substituted imidazole ring as well as a dichlorphenyl ring and some form of ether linkage. Doubling the heterocyclic ring, now replaced by 1,2,4-triazole, as well as replacing chlorine by fluorine leads to the very effective oral active antifungal agent **fluconazole** (**114-4**); this drug has proven particularly useful in treating the opportunistic fungal infections contracted by AIDS patients. The starting material (**114-1**) for the synthesis is available by acylation of *meta*-difluorobenzene with chloroacetyl chloride. The displacement of chlorine by triazole affords the intermediate
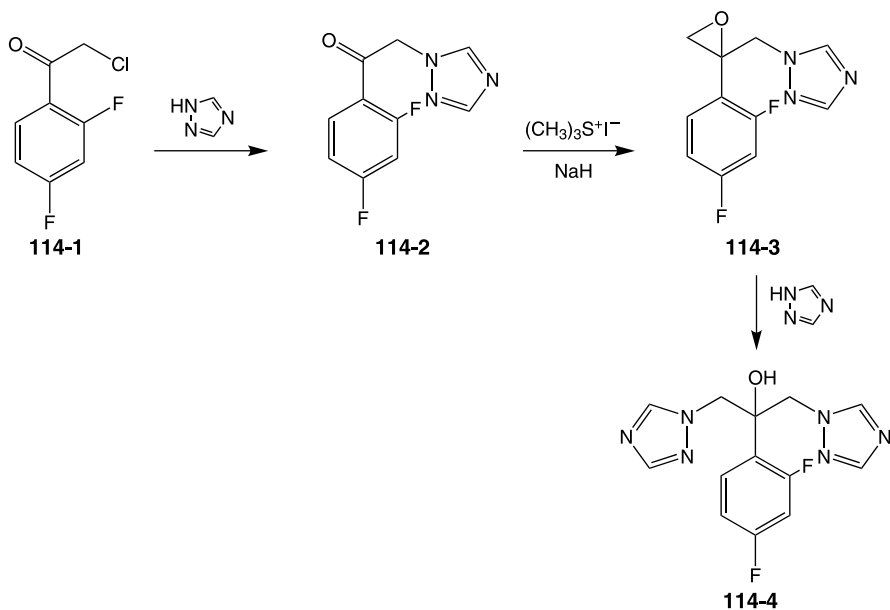
(**114-2**). Condensation of the carbonyl group with the ylide from trimethylsulfonium iodide leads initially to an addition product. The anion formed on the carbonyl oxygen then internally displaces dimethyl sulfide to give an oxirane yielding epoxide (**114-3**). Reaction of that intermediate with a 1,2,4-triazine leads to an epoxide ring opening with the consequent incorporation of the second heterocyclic moiety. There is thus obtained fluconazole (**114-4**) [125].

Activity is retained when one of the triazole rings in fluconazole is replaced by pyrimidine. The synthesis starts with the construction of that six-membered ring. Thus, condensation of β-ketoester (**115-1**) with formamidine leads to pyrimidine (**115-2**). Treatment of that intermediate with phosphorus oxychloride leads to the corresponding chlorinated compound (**115-3**). The addition of enolate from the treatment of the pyrimidine (**115-3**) with a strong base leads to an addition to the carbonyl group in fluconazole intermediate (**114-2**). The resulting tertiary alcohol (**115-4**) is obtained as a mixture of diastereomers. The chlorine atom, having served its function, is now removed by catalytic hydrogenation. Separation of the diastereomers followed by resolution of the desired enantiomer pair affords the antifungal agent **voriconazole** (**115-5**) [126].
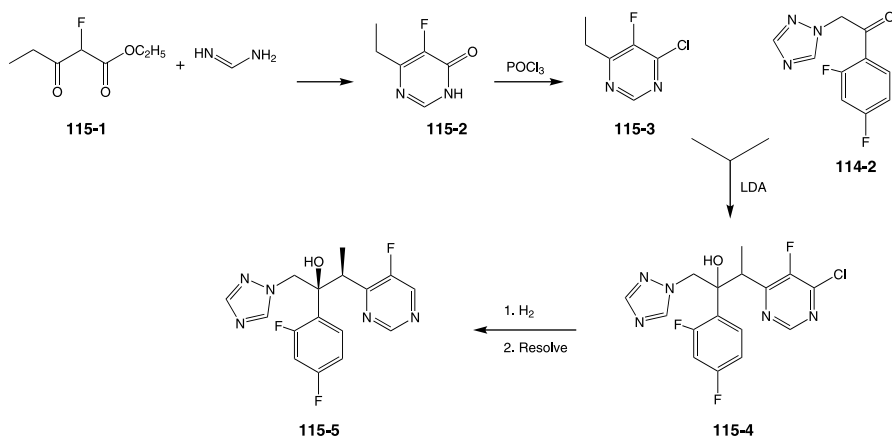
The first histamine H_2 antagonist, it will be recalled, retained the imidazole of histamine and achieved its blocking activity by the presence of a thiourea function. Both functions, it was later found, could be extensively modified. The thiourea group, as noted above, can be replaced by appropriately substituted guanidines or amidines that form part of a heterocyclic ring (see oxmetidine, **66-2**) and the imidazole replaced by other heterocycles. In the H_2 blocker **lavoltidine** (**116-8**), the last is replaced by a phenoxy benzylamine while an aminotriazole serves as a surrogate guanidine. The synthesis starts with the acylation of imine (**116-1**) with acetylglycolyl chloride (**116-2**) to give amide (**116-3**). The reaction of the intermediate with the N-methylhydrazone of benzaldehyde (**116-4**) leads to the amidine (**116-5**) by the displacement of one of the methylthio groups by means of an addition-elimination sequence. Treatment of the intermediate with the primary amine (**116-6**) leads to the replacement of the remaining thiomethyl group and the formation of guanidine

(**116-7**). Acid hydrolysis of the hydrazone leads to the corresponding hydrazine; the terminal amino group cyclizes with the carbonyl group to form a triazole ring. Saponification of the acetyl protecting group gives the corresponding free alcohol and thus **lavoltidine** (**116-8**) [127].

The use of estrogen antagonists, primarily tamoxifen, for treating breast cancers that exhibit estrogen receptors is based on the fact that such compounds diminish the hormonal stimulation that leads to the growth of cancerous tissue. Antagonists include the modified steroidal estrogen fluverestant (Chapter 4) and the half-dozen or so nonsteroidal antagonists detailed in Chapter 6. An alternative relies on cutting back on the endogenous levels of estrogens by inhibiting the synthesis of the hormone. These agents, dubbed aromatase inhibitors, act by preventing the conversion of an androgen that includes a angular methyl group at the A-B ring junction to a fully aromatic ring A devoid of that substituent. The synthesis of the aromatase inhibitor **letrozole** (**117-5**) starts by the displacement of bromine in the benzyl bromide (**117-1**) by the basic nitrogen in triazole (**117-2**) to afford the alkylation product (**117-3**). This product is then treated with a strong base to provide the benzylic carbanion. This in turn displaces fluorine in the benzonitrile (**117-4**) in a nucleophillic aromatic substitution reaction to afford the alkylation product (**117-5**) and thus letrozole [128].

Much the same activity is displayed in a compound in which the nitriles are attached to aliphatic (and highly sterically hindered!) carbon. The displacement of benzillic bromine from the mesytilene derivative (**118-1**) by treatment with potassium cyanide under phase transfer conditions affords the dinitrile (**118-2**). Exhaustive

methylation of this intermediate by treatment with methyl iodide and sodium hydride leads to the replacement of the side chain hydrogen atoms by methyl groups (**118-3**). Treatment of that intermediate with bromine in the presence of benzoyl peroxide leads to the formation of benzyl bromide (**118-4**). Reaction of that product with triazole in the presence of a base completes the synthesis of the aromatase inhibitor **anastrozole** (**118-5**) [129].
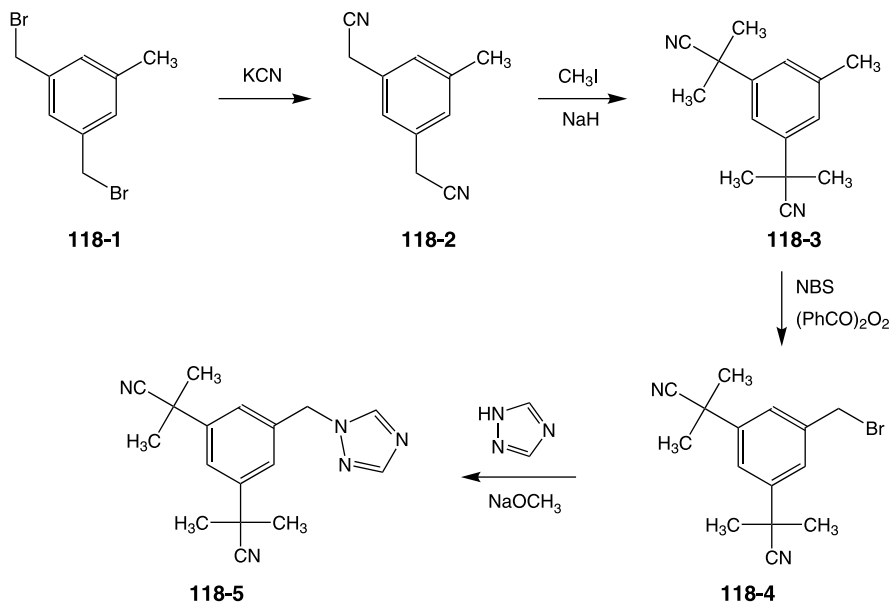
Arylpiperazines have a venerable history as psychotropic agents. One of these compounds that incorporates as well a 1,2,4-triazol-3-one ring shows significant anti-depressant activity. Reaction of propionamide (**119-1**) with phosgene leads to the corresponding imino chloride (**119-2**). Condensation of that intermediate with hydrazine methylurethane gives the corresponding guanidine (**119-3**) from the displacement of chlorine by basic hydrazine nitrogen. Reaction with sodium methoxide leads first to the ionization of the amine on the side chain; this then cyclizes to triazolone (**119-4**) by displacing the urethane methoxyl. Alkylation of the anion from the reaction of the triazolone with a strong base with chloride (**119-5**) affords **nefazodone** (**119-6**) [130].
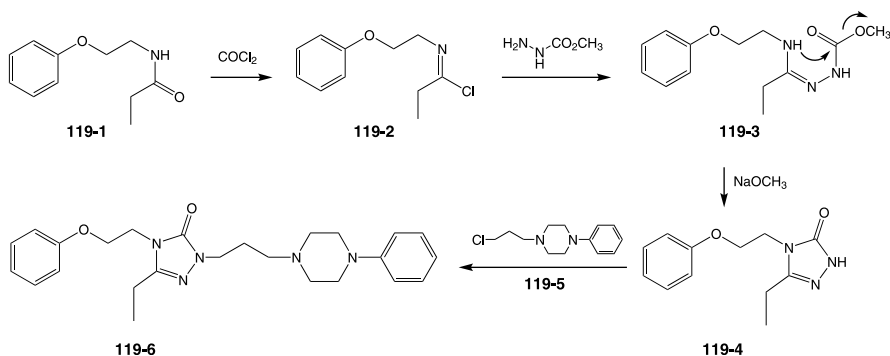
The virus that leads to AIDS is renowned for its ability to develop resistance to aniviral drugs. This has prompted the search for agents that act at different stages in the natural history of HIV in addition to those addressed by current drugs. A recent new class of agents depends on the fact that the viral infection starts by binding virions to specific receptor sites on the immune system cells in order to gain entry into those cells. The very recent antiviral agent **maraviroc** (**120-12**) binds with the same sites as HIV and thus prevents the very first stage in the process of infection. The synthesis of this agents starts by protection of the amino group in the bridged bicyclic amine (**120-1**) as its benzyl derivative (**120-2**). The carbonyl group at the other end of the molecule is then converted to its oxime (**120-3**). Treatment of that intermediate with sodium in alcohol reduces that group to a primary amine (**120-4**). Construction of the triazole ring starts with the acylation of the amine with the acid chloride from iso-butyric acid to form the isobutyramide (**120-5**). Reaction of that with phosphorus oxychloride converts the amide into the corresponding chlorinated imine (**120-6**). Treatment with acylhydrazide leads to addition-elimination of the basic hydrazide nitrogen to the imino chloride and thus the formation of the imino-amide (**120-7**). Heating in the presence of an acid leads to a reaction of the imino nitrogen with the carbonyl group. This closes the ring and affords the triazole (**120-8**). Catalytic reduction removes the benzyl protecting group, unmasking the basic ring nitrogen (**120-9**). In a converging scheme, the ester in the peptide-like fragment (**120-10**) is reduced to afford aldehyde (**120-11**). Reductive amination of this last amine (**120-9**) with sodium triacetoxy borohydride leads to the coupled product, maraviroc (**120-12**) [131].
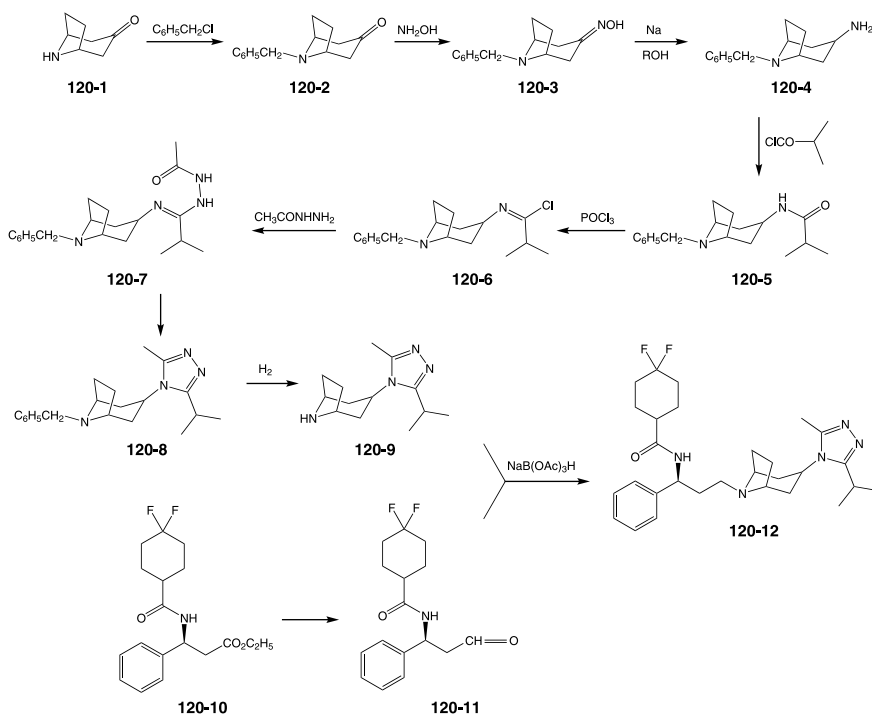
Inhibitors of protein kinases (PK) have provided the focus for considerable research due to the involvement of these enzymes in cell proliferation. An agent that shows preference for PKs in malignant cells would provide new and hopefully better tolerated antitumor drugs. The first step in the convergent synthesis of such an inhibitor comprises the displacement of the terminal methanesulfonate from the side chain in (**121-1**) by 1,2,3-triazine proper. Reductive removal of the protecting group leads to the free phenol (**121-2**). Preparation of the second moiety involves a reaction that is one of the classical methods for forming an oxazole: the reaction of halomethyl carbonyl group with an amide. Thus, condensation of the cinnamic amide (**121-3**) with 1,3-dichloro acetone leads to the formation of oxazole (**121-4**), which retains a leaving group for a displacement reaction. Treatment of (**121-4**) with the alkoxide from the treatment of (**121-2**) with a base leads to the corresponding ether, the PK inhibitor **mubritinib** (**121-5**) [132].
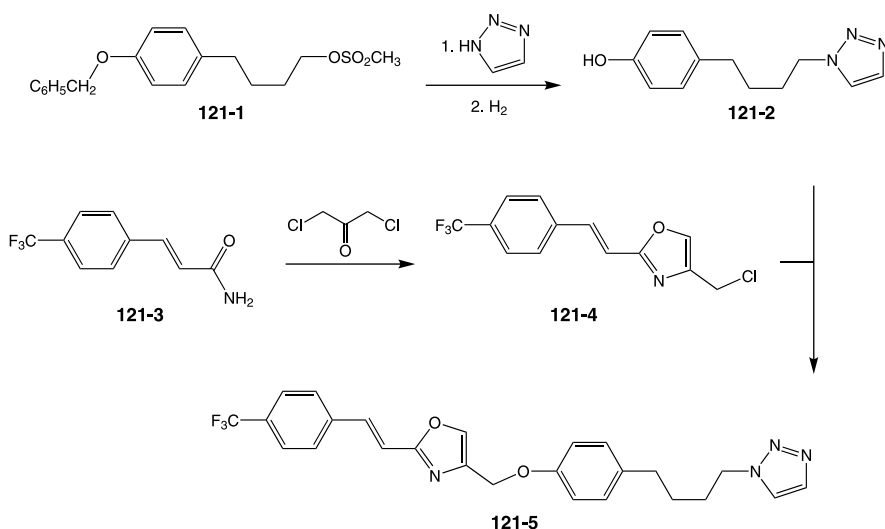
8.4.3. Thiadiazoles

The sequence of events that led from the observation of excess urine excretion on administration of high doses of sulfonamide antibacterial agents to the development of diuretic drugs was touched upon in Chapter 2. It is of interest that one of the first sulfonamide diuretic agents consisted of a compound in which the benzene ring of the antibacterial sulfonamides was replaced by a thiadiazine. Treatment of commercially available 1,3,4-thiadiazine (**122-1**) with acetic anhydride gives the corresponding acetamide (**122-2**). The mercapto group is then oxidized to a sulfonyl chloride (**122-3**) by reaction with aqueous chlorine, essentially hypochlorous acid. Ammonolysis of this last intermediate affords **acetozolamide** (**122-4**) [133].
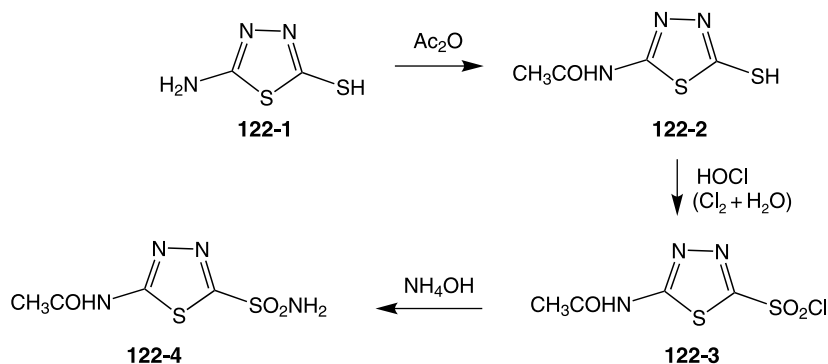
The sulfonylurea hypoglycemic agents, as noted in Chapter 2, also trace their ancestry to the sulfonamides. It is of interest that activity is retained when a substituted 2-amino-1,3,4-thiadiazole replaces the urea function. Reaction of isobutyryl chloride (**123-1**) with thiosemicarbazone (**123-2**) leads initially to the transient 1,2-diacylhydrazine (**123-3**). This apparently cyclizes spontaneously to thiadiazine (**123-4**) under reaction conditions. Acylation with *p*-methoxysulfonyl chloride (**123-5**) affords the oral hypoglycemic agent **isobuzole** (**123-6**) [134].
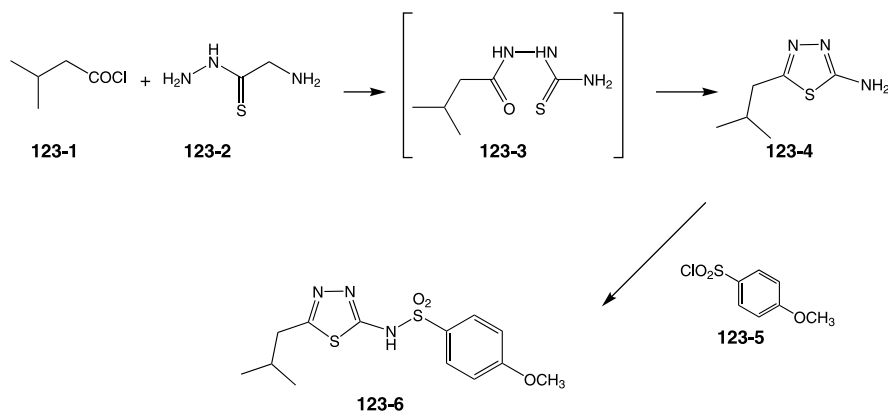
The increasing availability of practical enantioselctive synthetic methods has combined with a growing awarness of the stereospecifc nature of drug action to place new regulatory emphasis on providing drugs in chiral form. The synthesis of the β-blocker **timolol** (**124-8**) illustrates an entantiospecific synthesis. Preparation of the 1,3,5-tiadiazine intermediate (**124-4**) involves the reaction of the cyanoamide (**124-1**) with sulfur monochloride. The reaction can be rationalized by invoking the addition of the reagent across the nitrile group to form an intermediate such as (**124-2**). Displacement of the chlorine on sulfur by the amide nitrogen serves to close the ring; tautomerization to the all-enol form then gives the observed product (**124-3**). The hydroxyl is then converted to its *para*-toluenesulfonate (**124-4**). The key to the synthesis involves the preparation of the propyl aminoalcohol side chain by use of a chiral starting material. The required side chain glycol R-glyceraldehyde

(**124-5**) is available in chiral form as a degradation product from the sugar mannitol, which consitutes a tonnage chemical. Thus, reductive amination of the aldehyde with *tert*-butylamine gives the ethanolamine side chain (**124-6**) in chiral form. Displacement of the tosylate with the terminal alkoxide from diol (**124-6**) incorporates the propanolamine side chain to give (**124-7**). Replacement of the remaining leaving group on the heterocycle chlorine by morpholine affords **timolol** (**124-8**) [135], a drug used in the form of eyedrops for lowering intraocular pressure due to glaucoma.
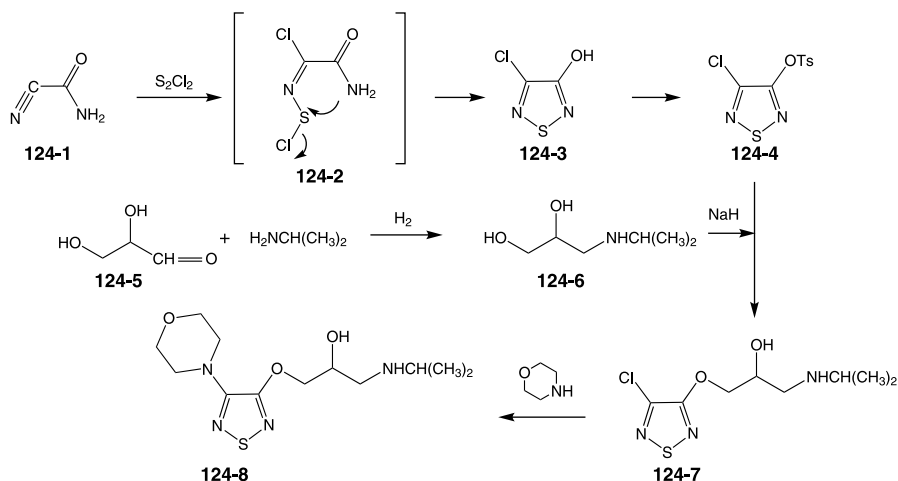
8.4.4. Tetrazoles

The presence of the propionamide fragment in the structure of the anti-inflammatory agent **broperamole** (**125-1**) is reminiscent of the heterocycle-based NSAID propionic acids. The activity of this agent may trace back to the acid that would result on hydrolysis of the amide. Tetrazoles are virtually always prepared by reaction of a nitrile with hydrazoic acid or, more commonly, sodium azide in the presence of acid in a reaction very analogous to a 1,3-dipolar cycloaddition. A more recent (and safer) version of the reaction noted later (see losartan, **77-4**) uses tributyltin azide. In the case at hand, reaction of the anion of *meta*-bromobenzonitrile (**125-1**) with sodium azide and an acid affords the tetrazole (**125-2**). Condensation of the anion from that intermediate with ethyl acrylate leads to the product from Michael addition; saponification gives the corresponding carboxylic acid (**125-3**). This is then converted to the acid chloride; reaction with piperidine affords **broperamole** (**125-4**) [136].
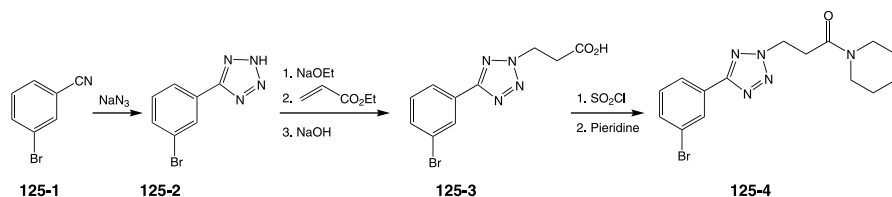
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CHAPTER 9

DRUGS BASED ON SIX-MEMBERED HETEROCYCLES

Six-membered heterocyclic rings play much the same diverse roles on biological activity as their five-membered counterparts. In many cases these serve as simple platforms for functional groups or in other instances provide a basic function. Those moieties can alternatively form a part of a pharmacophore.

9.1. RINGS THAT CONTAIN ONE HETEROATOM

9.1.1. Pyrans

Thromboxane A_2 (TXA$_2$), a product of the arachidonic cascade, comprises one of the most potent of the known platelet aggregating agents. A bridged bicylic pyran that mimics part of a thromboxane structure, which also features prostaglandin-like side chains, acts as a TXA$_2$ receptor binding antagonist. The starting cyclic lactol (**1-1**) can in principle be obtained in several steps from the Diels-Alder product from furan and maleic anhydride. Reaction with the Grignard reagent (**1-2**) from the silyl ether of 2-bromo(3-hydroxypropyl)benzene leads to the adduct (**1-3**), no doubt via the small amount of hydroxyladehyde in equilibrium with the lactol. The first-formed adduct cyclizes to the tetrahydrofuran under reaction conditions or on workup. Catalytic hydrogenation then reduces the benzylic carbon-oxygen bond opening the fused furan to afford the hydroxymethyl derivative; this is then acylated with acetic anhydride to give (**1-4**). Treatment with acid then serves to uncover the hydroxyl group on the three-carbon side chain. Sequential oxidation with Jones

reagent followed by esterification with methanolic hydrogen chloride leads to the ester (**1-5**); the pendant acetoxy group is deacylated in the process. A second round of Jones reagent then converts that group to an acid as well (**1-6**). This carboxyl group is next coupled in the presence of dicyclohexyl carbodiimide (DCC) with the pentylamide derivative (**1-7**) from serine to from the amide (**1-8**). Treatment with methanesulfonyl chloride converts the hydroxyl from serine to a good leaving group. This cyclizes to an oxazoline (**1-9**) in the presence of triethylamine via the enol form of the adjacent amide. Treatment of this last intermediate with cuprous bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) oxidizes the newly formed heterocycle to an oxazole. Saponification then completes the synthesis of the TXA$_2$ inhibitor **ifetroban** (**1-10**) [1].
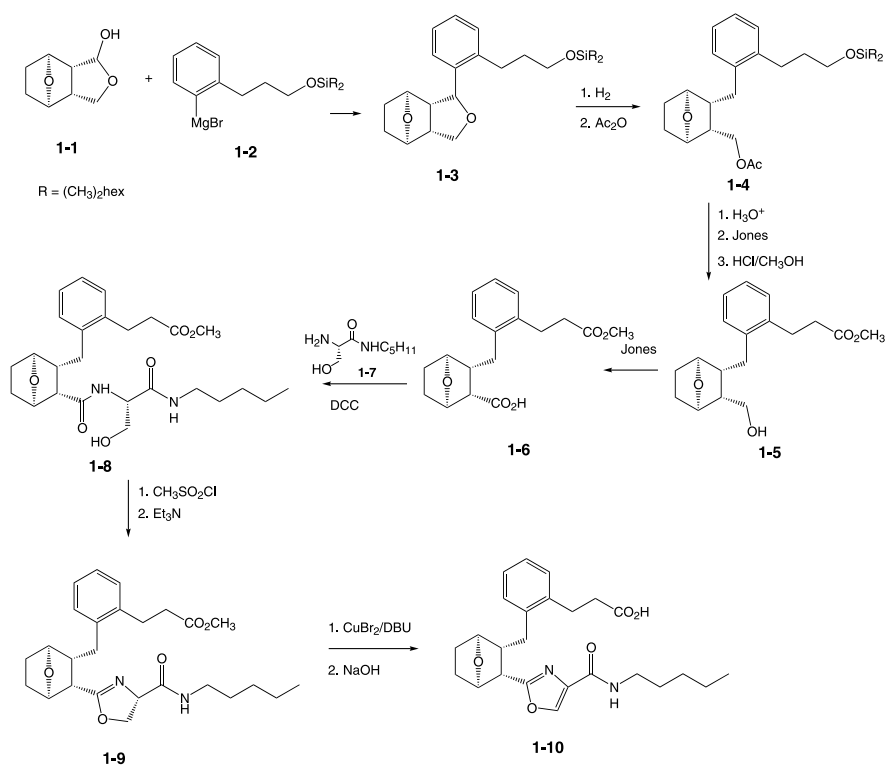
Outbreaks of avian influenza starting near the beginning of the present century have posed the danger of a pandemic of disease comparable to that which swept the world in the late teens of the twentieth century. Dire results have been predicted should the virus mutate so as to be readily transmitted to, and by, humans. The research occasioned by this threat has led to several compounds that halt the replication of the influenza A (H5N1) virus. The final step in the replication of the virus comprises the extrusion of new virions from infected cells by way of buds on the cell membrane. The proteolytic enzyme sialidase, also known as neuramindase,

cuts the base of the buds, allowing the release of the newly formed virions. A complex tetrahydropyran whose structure incorporates many of the features of neuraminidase itself effectively blocks the enzyme. The synthesis of this antiviral agent begins by protection of commercially available N-acetylneuramic acid (**2-1**) by sequential esterification with methanol in the presence of an ion-exchange resin followed by acylation with acetyl chloride (**2-2**). Reaction of that intermediate with hydrogen chloride then replaces the free tertiary hydroxyl by chlorine (**2-3**). Treatment of that product with the base DBU leads to the dehydrochlorination and introduction of the conjugated unsaturation (**2-4**). Boron trifluoride then causes enol oxygen from the enolic form of the acetamide to displace the adjacent acetoxy function with the consequent formation of the fused oxazoline ring (**2-5**). Solvolysis in acetic acid restores the hydroxyl with, however, an inverted configuration (**2-6**). This last intermediate is then allowed to react with diphenylphosphinous azide. This reagent in essence displaces the free hydroxyl by a backside attack to afford the azide (**2-7**); the configuration at the reaction center is again inverted in the process leading to the net inversion of that center from that in the starting material (**2-1**). Treatment of the product with hydrogen sulfide in pyridine serves to reduce the azide group to a primary amine (**2-8**). Reaction of that intermediate with N-pyrrazologuanidine (**2-9**) leads to an exchange of the primary amine and adding the requisite guanidine group. Saponification removes the protecting groups to afford **zanamivir** (**2-10**) [2].
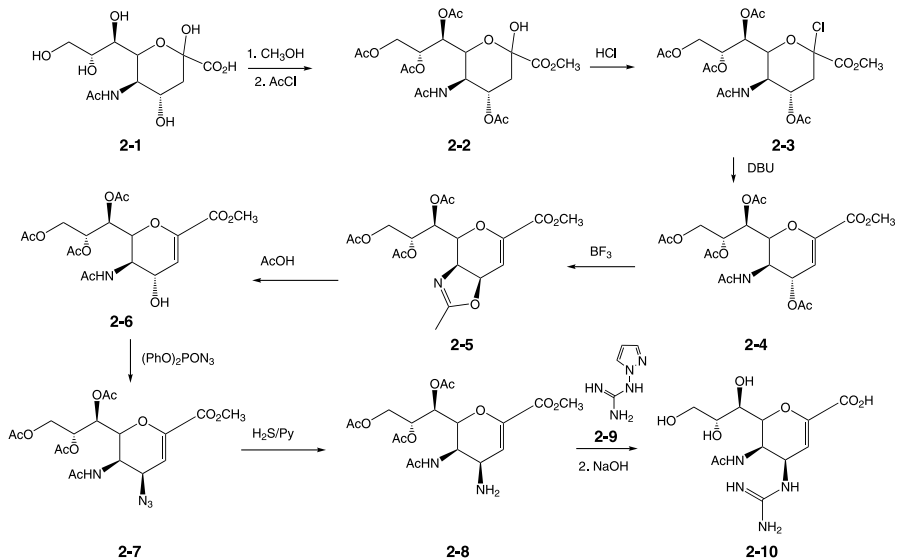
Several carbocylic analogues of zanamivir that have been developed subsequently that display the same antiviral activity as zanamivir. The importance of the first of these, **oseltamivir**, more familiarly known as Tamiflu®, has attracted the attention of academic chemists. Departing briefly from the organizing principle of this book,

the synthesis of one of those is presented here since it involves particularly elegant chemistry. The resulting approach is notable in that it does not involve a difficult-to-obtain natural product starting material ($515/gram) and completely obviates the use of potentially explosive azide intermediates. The first step involves building the carbocyclic ring equipped with a chiral carbon atom that will determine the stereo-chemistry of the many remaining ring substituents. Thus, $2 + 4$ cycloaddition of acrylate (**3-1**) to butadiene in the presence of the pyrrolidine derivative (**3-2**), as a chiral catalyst, affords the ester (**3-3**) as a virtually optically pure isomer. The ester group is then converted to an amide (**3-4**) by simple interchange with ammonia. Reaction with iodine under special conditions leads to the nitrogen counterpart of an internal iodo-lactonization reaction, affording the bridged iodolactam (**3-5**). The amide nitrogen is then protected as its *tert*-butoxycarbonyl derivative (**3-6**). Dehydroiodination with DBU introduces a double bond, giving (**3-7**). Free radical bromination of that intermediate with *N*-bromosuccinimide proceeds with the shift of the olefin to give the allylic bromide (**3-8**). Dehydrobromination with cesium oxide introduces an additional double bond in the ring. The presence of ethanol leads the lactam ring to open at the same time (**3-9**). The second nitrogen required for the product is introduced by an unusual novel reaction. Thus treatment of diene (**3-9**) with acetonitrile and *N*-bromosuccinimide in the presence of stannic bromide introduces the requisite additional nitrogen. The transform can be rationalized by positing an initial addition of bromide to the olefin to form a cyclic bromonium ion; addition of the unshared pair of electrons on the nitrile nitrogen would then account for the connectivity. Hydrolysis of the initial imine-like intermediate would account for the observed product (**3-10**). Treatment with a base then leads to the internal displacement and formation of the aziridine ring in (**3-11**). Reaction with 3-pentanol followed by removal of the BOC group then affords oseltamivir (**3-12**) [3].
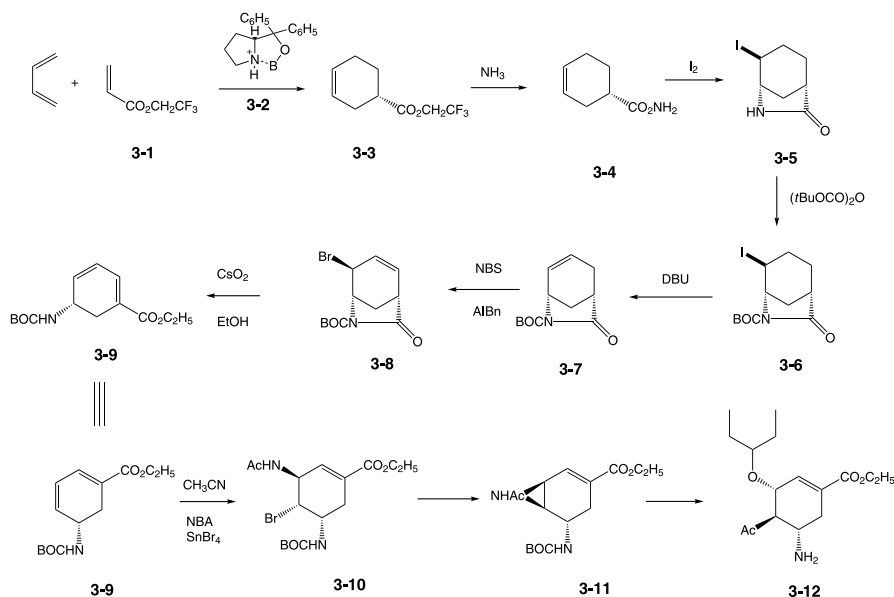
9.1.2. Pyridines

The unmodified pyridine ring, in contrast to imidazole or imidazoline rings, is seldom associated with any specific pharmacophoric activity. It does, however, appear in a number of therapeutic agents due to the fact that benzene rings in biologically active compounds can often be replaced by pyridines in spite of the presence of the basic nitrogen atom. The relatively small number of pyridines discussed below thus do not reflect the frequency of their occurrence in therapeutic agents; instead, examples have been selected that illustrate some facet of pyridine chemistry.

The micobacterium that causes tuberculosis is extremely resistant to most antibacterial agents. The discovery that a very simple derivative of pyridine, **isoniazid** (pyridine-4-carboxylic acid hydrazide), showed antibacterial activity against that microbe permitted major inroads against that disease in Western society. The structurally related thioamide **ethionamide** (**4-7**) has also proven to be active against tuberculosis in humans. One synthesis of this agent starts with the aldol condensation of diethyl oxalate with 2-butanone to give the diketo-ester (**4-1**). Condensation of that compound with cyanoacetamide (**4-2**) leads to pyridone (**4-3**), depicted as its unconjugated tautomer. The reaction can be visualized as involving an initial conjugate addition of the cyanoacetamide anion to (**4-1**), followed by the elimination of hydroxide; internal imine formation then closes the ring. Hydrolysis of the intermediate leads to a β-ketoacid, which then loses carbon dioxide under the reaction conditions to afford the pyridone acid (**4-4**). Treatment of that product with phosphorus oxychloride converts the amide to its imino chloride; the carboxyl group is converted to the acid chloride under reaction conditions. Exposure of the first-formed product to ethanol then gives the ester (**4-5**). The ring chlorine is then removed by catalytic hydrogenation and the ester exchanged to an amide with ammonia to give (**4-6**). The two-step sequence used originally [4] to convert that function to a thioamide would be now be accomplished directly with phosphorus pentasulfide to give **ethionamide** (**4-7**).
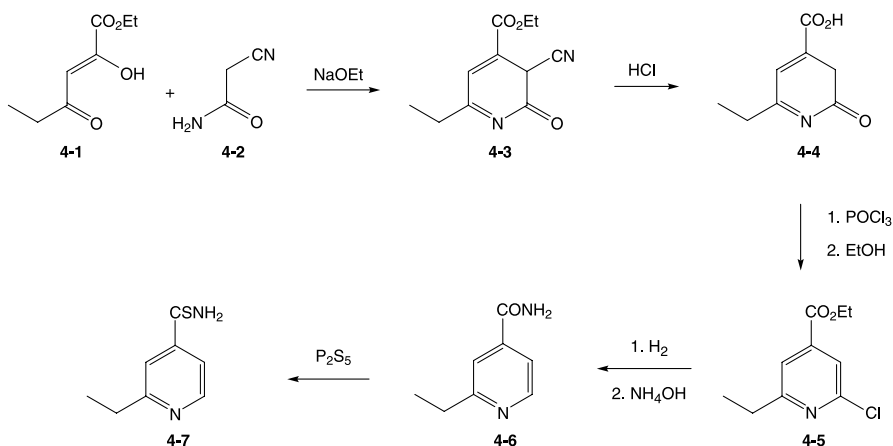
One broad category of NSAIDS, discussed in Chapter 2, comprises *N*-arylanthranilic acids and their "fenac" homologues. As an example of the equivalence of benzene and pyridine rings noted above, cyclooxygenase inhibiting activity is retained when the ring bearing the carboxylic acid is replaced by pyridine. The key reaction to the series involves the treatment of nicotinic acid *N*-oxide (**5-1**) with phosphorus oxychloride. This results in the chlorination of the adjacent ring carbon with a loss of oxygen in a Polonovski-like rearrangement. The regiochemistry is probably dictated by migration to the center with lower electron density. Nucleophilic aromatic displacement of that chlorine with *meta*-trifluoromethylaniline (**5-3**) leads to the diaryl amine and thus **nifluminic acid** (**5-4**) [5]. The closely related compound **flunixin** (**5-6**) has much the same activity. Preparation of this last agent is analogous to that for (**5-4**), replacing the aniline (**5-3**) by its analogue (**5-5**), which has a methyl group at the 2 position [6].
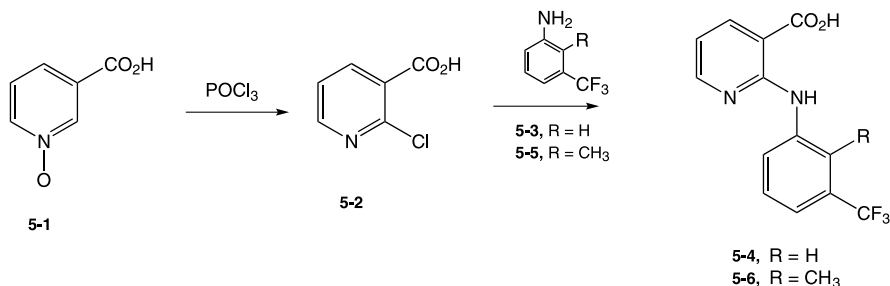
It was noted in Chapter 2 that the interposition of a methylene group between the benzene ring and the *meta* hydroxyl in β-adrenergic agonists led to very potent compounds, exemplified by the widely used bronchodilator **albuterol**. Activity is retained, in this case as well, when benzene is replaced by pyridine. Reaction of 3-pyridinol benzyl ether (**6-1**) with formaldehyde and a strong acid leads to the *bis*-hydroxymethylation product (**6-2**). In the key reaction, treatment of that diol with manganese dioxide can be controlled to give the product (**6-3**) from selective oxidation of the more sterically accessible hydroxyl group. Addition of the anion from nitromethane to the carbonyl group results in the formation of the intermediate (**6-4**), which now
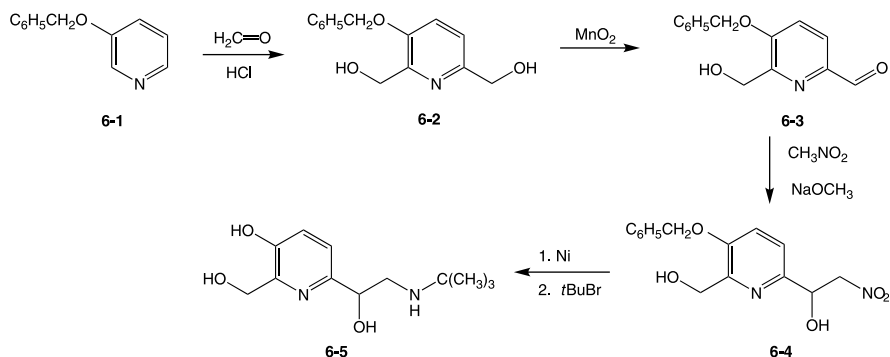
has the requisite side chain carbon atoms. The nitro group is then reduced by means of Raney nickel and the resulting primary amine alkylated with *tert*-butyl bromide. Hydrogenolysis over palladium then removes the benzyl protecting group to afford the β-adrenergic agonist **pirbuterol** (**6-5**) [7].

A simplified derivative of **quinine** in which a substituted pyridine replaces quino-line retains the antimalarial activity of the parent drug (see Chapter 11). The highly substituted pyridine ring is formed in this case by reaction of aroyl acrylic acid (**7-1**) with acyl pyridinium salt (**7-2**) and ammonium acetate in a version of the Kroehnke reaction. The reaction can be visualized as starting with the formation of an anion (or ylide) at the highly activated acyl methylene group on (**7-2**). This then adds to the enone function in (**7-1**); loss of the excellent leaving group, pyridine, leads to the formation of the hypothetical intermediate (**7-3**). The ammonia in the reaction medium then converts the 1,5-diketone to a pyridine ring, yielding the intermediate (**7-4**). Condensation of the carboxyl group in the latter with 2-lithiopyridine from halogen exchange from 2-bromopyridine and butyl lithium then affords the diaryl ketone (**7-4**). Basic nitrogen in the terminal ring of the final product mimics nitrogen on the quinuclidine ring in **quinine**. The discrimination between the two pyridine rings in (**7-4**) required for selective reduction of a single ring depends on the relatively higher basicity of the terminal ring since it contains fewer electron-withdrawing substituents than does the central pyridine ring. Thus, catalytic hydrogenation of (**7-4**) in the presence of acid leads to a reduction of the protonated ring. The ketone is reduced to an alcohol in the same reaction. Isolation of the *R*, *R* isomer by fractional crystallization and affords **enpiroline** (**7-5**) [8].
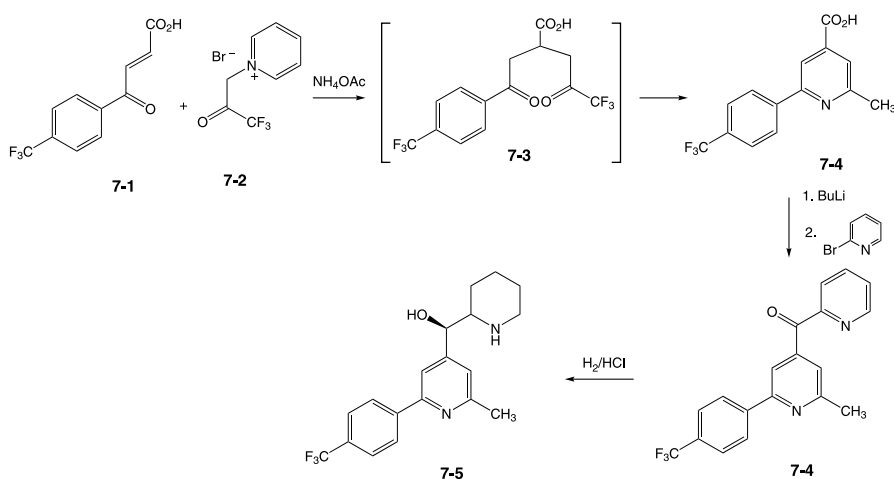
Virtually all of the older antiallergic H_1 antihistamines show significant sedation as a side effect; many over-the-counter sleep aids in fact simply comprise one of these older antihistamines. The finding that this class of drugs can act directly on the allergic end target organs has led to the development of a spate of polar anti-histamine drugs that do not cross the blood–brain barrier and consequently cause

no, or much diminished, CNS-mediated sedation. The majority of these drugs are kept out of the CNS by incorporating polar carboxylic acid moieties. The synthesis of one of these compounds, **acrivastine (8-7)**, starts by addition of the mono-lithio derivative from 2,5-dibromopyridine (**8-1**) to 4-toluonitrile (**8-2**). Hydrolysis of the first-formed imine with a dilute acid leads to the diketone (**8-3**). This is then condensed with the ylide from triphenyl-2-*N*-pyrrolidylethylphosphonium bromide (**8-4**) to give the olefin (**8-5**) as a mixture of geometric isomers. The remaining bromine on the pyridine ring is then converted to its lithio reagent by halogen exchange. Reaction of the latter with dimethyl formamide leads to the incorporation of a formyl group and the formation of the intermediate (**8-6**). Horner-Wadsworth condensation of the carbonyl group leads to the formation of an acrylic acid side chain; the product from the last reaction probably consists largely of the *trans* isomer. The *E,E*-isomer is then separated to afford **acrivastine (8-7)** [9].
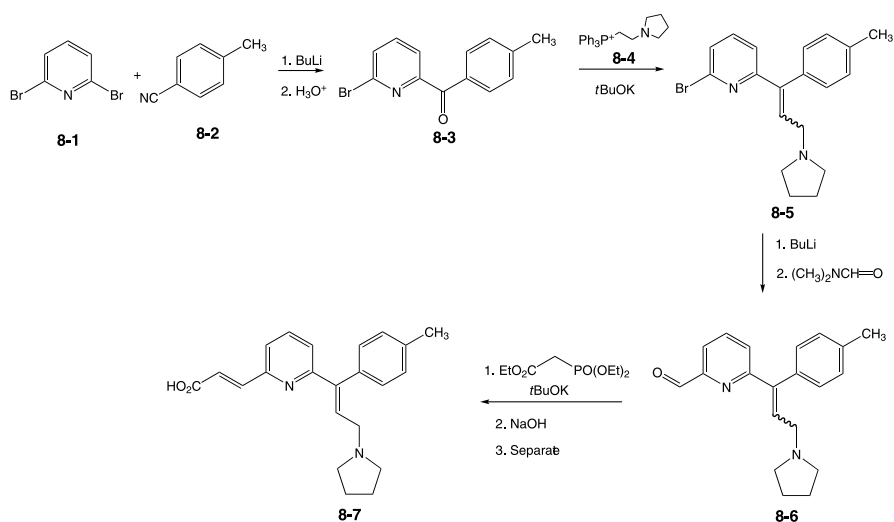
Many, if not most, leukotrienes receptor antagonists are based on benzene rings (see pobolukast *et seq.* in Chapter 2). In contrast to those agents, the receptor antagonist **ticolubant (9-10)**, which is based on a central pyridine ring, is interestingly described as a compound that manifests anti-inflammatory activity. Condensation of the ylide from trimethyl phosphonoacetate with the pyridinealdehyde (**9-1**) leads to the acrylate (**9-2**). In a variant of the Mitsonobu reaction, the pyridol (**9-2**) is treated with 2-phenylethanol (**9-3**) in the presence of DEAD and triphenylphosphine to afford the phenyl ether (**9-4**). Oxidation with *meta*-chloroperbonzoic acid then converts the pyridine nitrogen to the corresponding *N*-oxide (**9-5**). That intermediate then undergoes the Polonovsky rearrangement when treated with trifluororacetic anhydride to afford the product where the adjacent methyl group is oxidized to an alcohol (**9-6**). Reaction with thionyl chloride replaces the newly formed hydroxyl by chlorine (**9-7**). Treatment of this last intermediate with

2,5-dichlorothiophenol (**9-8**) in the presence of a base displaces the halogen to afford the coupling product (**9-9**). Saponification of the ester function completes the synthesis of **ticolubant** (**9-10**) [10].
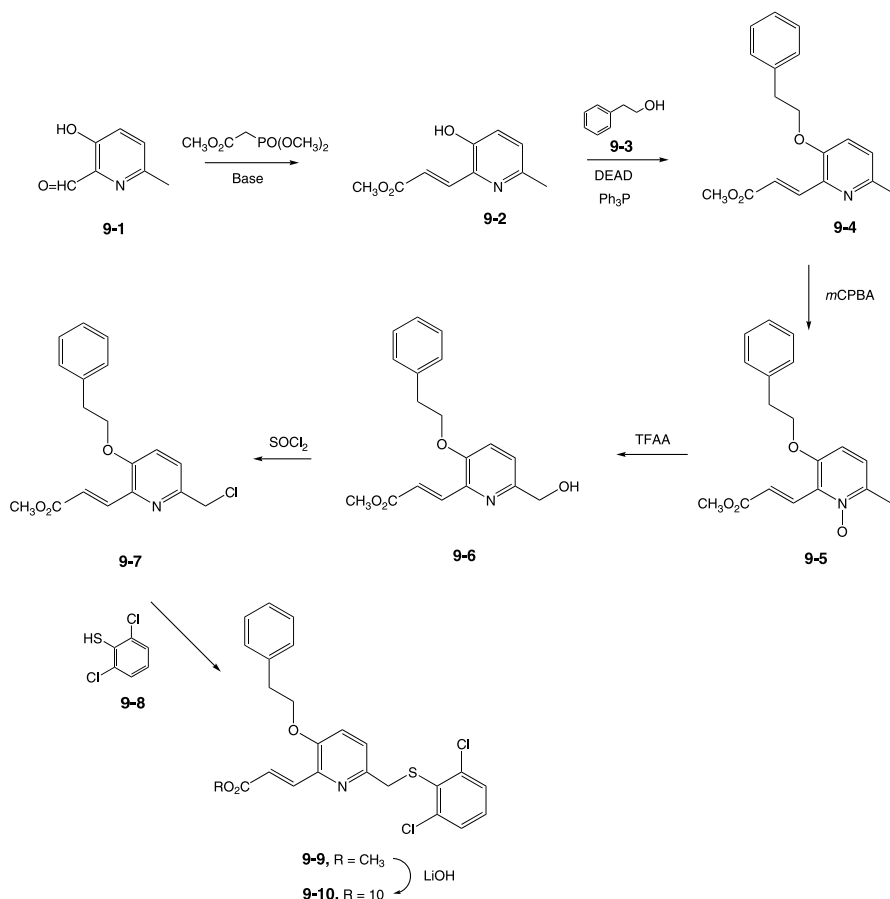
Agents that interact with cholinergic receptors have been extensively investigated for the treatment of Alzheimer's disease. One approach involves the administration of agents that bind to cholinergic nicotinic receptors. A compound closely related structurally to nicotine (**10-1**) is currently being investigated in the clinic. The synthesis of this agent starts with the dihalogenated pyridine (**10-2**) obtained from nicotine. Coupling this with the monosilyl derivative from acetylene in the presence of palladium : tetrakis triphenyl phosphine and copper iodide replaces iodine on the aromatic ring by the acetylene moiety (**10-3**). The remaining chlorine on the pyridine ring is then removed by reduction with zinc in acetic acid (**10-4**). The silyl protecting group is then cleaved with a fluoride ion to afford **altinicline** (**10-5**) [11].

10-1

10-2

Pd(Ph₃P)₄Cl
CuI

iPr_3Si——≡

10-3

Zn
AcOH

10-4

Bu₄N⁺ F⁻

10-5
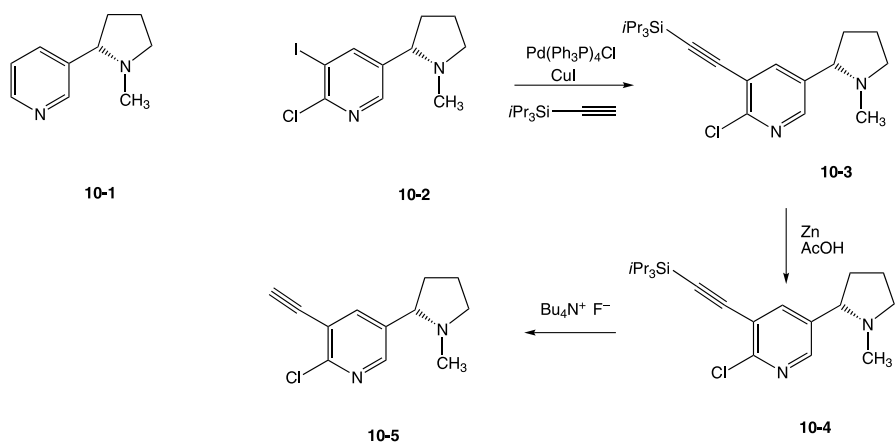
Nicotinaldehyde (**11-1**) serves as a starting material for a pair of closely related cholinergic agents that act on muscarinic receptors. The first step in the synthesis comprises the conversion of the aldehyde to its α-aminonitrile derivative (**11-2**) with potassium cyanide and ammonium chloride, in effect, ammonia and hydrogen cyanide. Reaction of that intermediate with sulfur chloride leads to the formation of the thiadiazole ring (**11-3**). Chlorine on the five-membered ring is the displaced by the alkoxide from 1-hexanol (**11-4**) to give the ether (**11-5**). The nitrogen on

11-1

KCN
NH₄Cl

11-2

S₂Cl₃

11-3

11-4

11-7

11-5

1. CH₃I
2. NaBH₄

11-8

1. CH₃I
2. NaBH₄

11-6

11-9
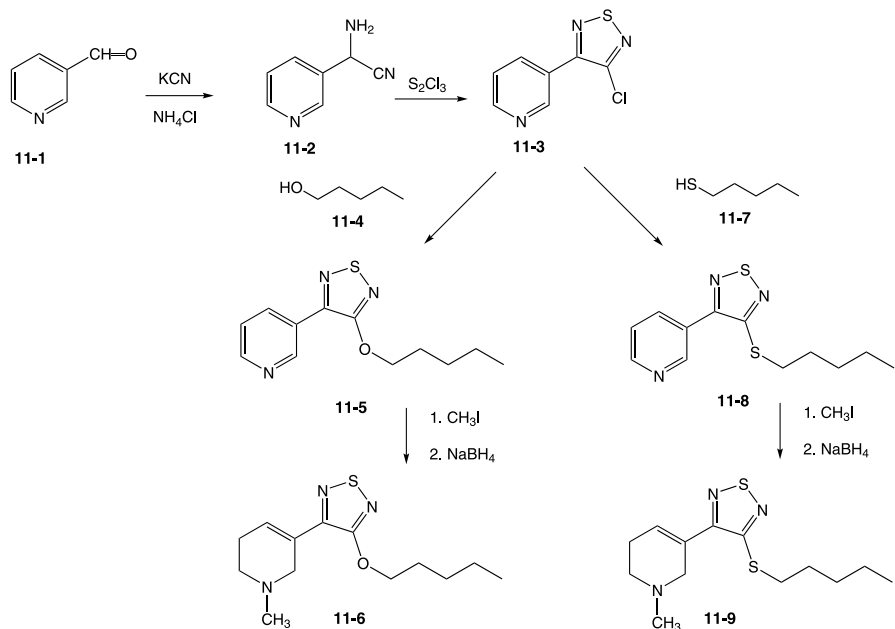
the pyridine ring is then alkylated with methyl iodide to yield the corresponding tenary imminium salt. Treatment of that salt with borohydride leads to the tetrahydro-pyridine in a reaction characteristic of that function (see, for example, the morphinans in Chapter 7). There is thus obtained **xanomeline** (**11-6**). The sequence (**11-3**) on using hexanethiol (**11-7**) as the alkylating agent leads first to the thioether (**11-8**). Treatment of that intermediate with methyl iodide followed by borohydride affords **tazomeline** (**11-9**) [12].

9.1.3. 1,4-Dihydropyridines

Calcium ions (Ca^{++}) play a pivotal role in a host of biological responses and particu-larly those involved in muscle contraction. Elevated intracellular levels of the ion have been found to be associated with muscular contraction. Excitation-induced movement of calcium ions into the cell can lead to inappropriate contractions of smooth muscle in the cardiovascular system. This is often manifested in the pathol-ogy that leads to spasms of coronary vessels that shows up as anginal pain; chroni-cally contracted vascular musculature can also be expressed as hypertension. Three structurally very diverse classes of drugs have all been shown to relax vascular smooth skeletal muscle by acting specifically on calcium movement in those tissues. These drugs, variously known as calcium antagonists, calcium blockers, or calcium channel blockers, comprise **verapamil** and its analogue (see Chapter 2), the benzo-1,5-thiazepine related to **diltiazem** (see Chapter 12) and the 1,4-dihydro-pyridines. By far the largest groups of calcium blocker analogue series fall into the last category, possibly because of their accessibility.

The great majority of 1,4-dihydropyridines are prepared using classical Hantzsch pyridine synthesis or one of its variants. The first dihydropyridine was in fact isolated back in 1882 as a stable intermediate from that method. In its simplest form, the syn-thesis involves heating an aldehyde such a *ortho*-nitrobenzaldehyde (**12-1**) with ethyl acetoacetate (**12-2**) and ammonia. The reaction almost certainly involves, as the first
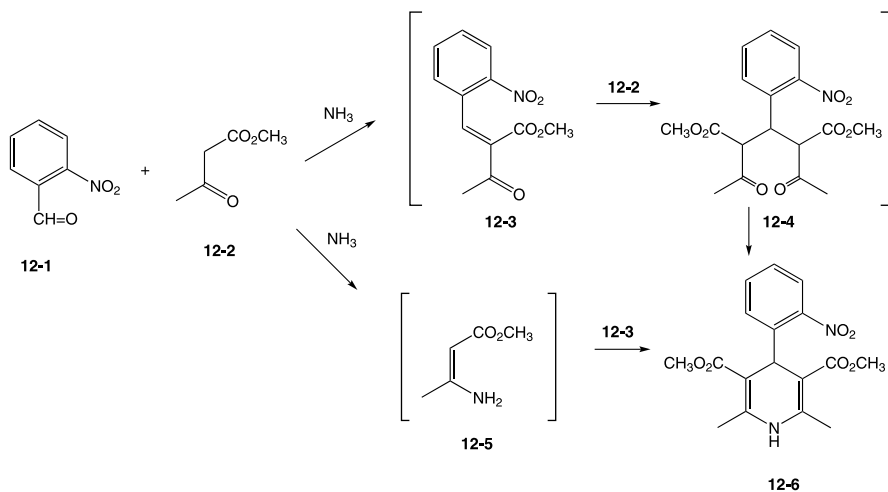
step, aldol condensation to form the benzylidene derivative (**12-3**). Conjugate addition of a second mole of acetoacetate would then afford the 1,5-diketone (**12-4**). Reaction of the carbonyl groups with ammonia will lead to the formation of the dihydropyridine ring. Alternatively, acetoacetate may go on to form the imine (**12-5**); reaction of this with the aldol product (**13-3**) will give the same dihydropyridine. The product, **nifedipine** (**12-6**) [13], has been used extensively for the treatment of angina and hypertension.

Extensive structure activity relationship (SAR) studies in this series revealed that unsymmetrical substitution on the heterocyclic ring and hence the introduction of chirality on the central carbon atom led to increased potency. Such asymmetrical dihydropyridines can be prepared by stepwise variation of the Hantzsch synthesis, based on the hypothetical alternate route to nifedipine. Thus, aldol condensation of methyl acetoacetate with 2,3-dichlorobenzaldehyde (**13-1**) gives the cinnamyl ketone (**13-2**). Reaction of that with the enamine (**13-3**) from ethyl acetoacetate gives the calcium channel blocker **felodipine** (**13-4**) [14].
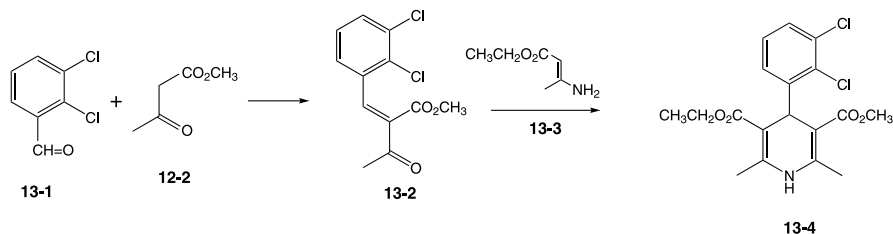
The key acetoacetate (**14-2**) for the synthesis of **nimodipine** (**14-5**) is obtained by alkylation of sodium acetoacetate with 2-methoxyethyl chloride. Aldol condensation of *meta*-nitrobenzene (**14-1**) and the subsequent reaction of the intermediate with eneamine (**14-4**) give nimodipine (**14-5**) [15].
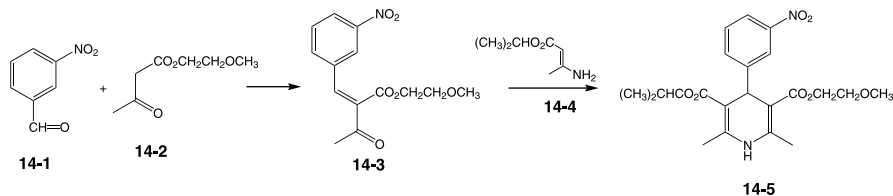
The product (**15-2**) from aldol condensation of *meta*-nitrobenzaldehyde with the dimethyl acetal from ethyl 4-formylacetoacetate (**15-1**) provides the starting material for a dihydropyridine in which one of the methyl groups is replaced by a nitrile. Reaction of (**15-2**) with the eneamine from isopropyl acetoacetate gives the corresponding dihydropyridine; hydrolysis of the acetal function with aqueous acid affords the aldehyde (**15-3**). That function is then converted to its oxime (**15-4**) by reaction with hydroxylamine. Treatment of that intermediate with hot acetic acid leads the oxime to dehydrate to a nitrile. There is this obtained **nilvadipine** (**15-5**) [16].
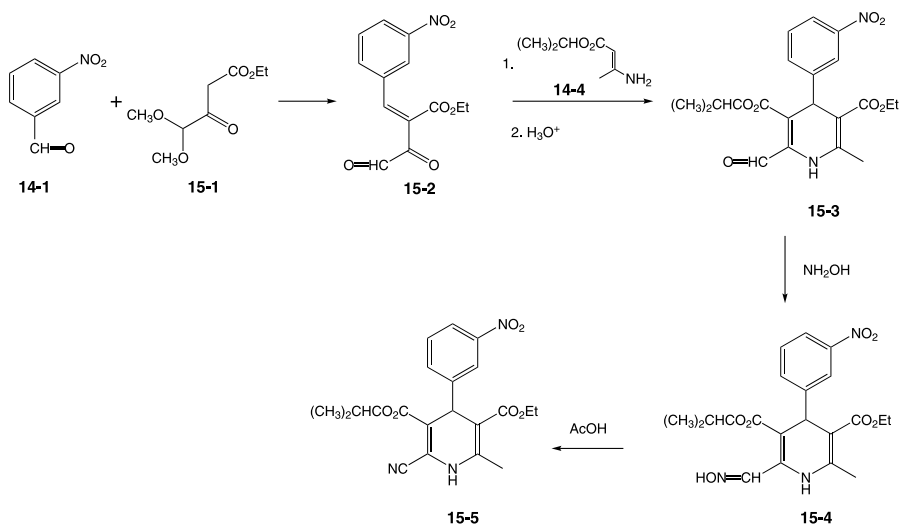
One approach to dihydropyridines substituted on ring nitrogen consists in simply alkylating the corresponding dihydropyridine on the ring nitrogen. Thus, reaction of the dihydropyridine from the Hantzsch synthesis of *meta*-trifluoromethyl benzaldehyde (**16-3**) with halide (**16-1**) in the presence of sodium hydride leads to directly to **flordipine** (**16-5**). An alternate approach relies on the stepwise formation of the dihydropyridine ring. This convergent scheme involves the alkylation of the eneamine (**13-3**) from ethyl acetoacetate with the chloroethylmorpholine (**16-1**) to give the intermediate (**16-2**). Reaction of that with the aldol condensation product (**16-4**) from aldehyde (**16-3**) and acetoacetate again leads to **flordipine** (**16-4**) [17].
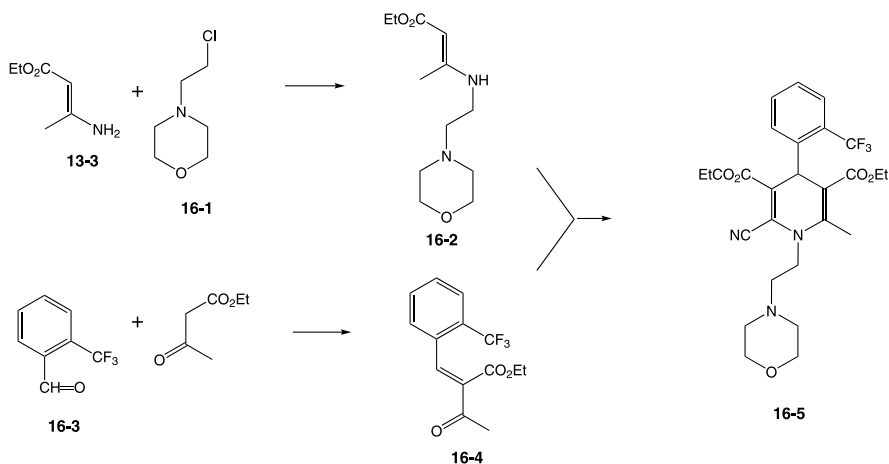
The synthesis of two rather complex dihydropyridines starts with the Wittig condensation of phthalaldehyde (**17-1**) with the ylide from triphenylphosphonium salt (**17-2**). The *trans* stereochemistry of the product (**17-3**) follows from the fact that the reaction is not carried out under salt-free conditions; selectivity for mon-oalkylation is probably due to steric hindrance from the newly introduced adjacent side chain at the alternate formyl group. Reaction of that intermediate with ethyl acetoacetate and ammonia gives the dihydropyridine **lacidipine** (**17-4**) [18]. Further modification of this compound depends on the allylic nature of the ring methyl groups. Thus reaction of (**17-4**) with pyridinium perbromide leads to the bro-mination of one of those groups and the formation of (**17-5**). The displacement of halogen by dimethylamine leads to the tertiary amine **taludipine** (**17-6**) [19].
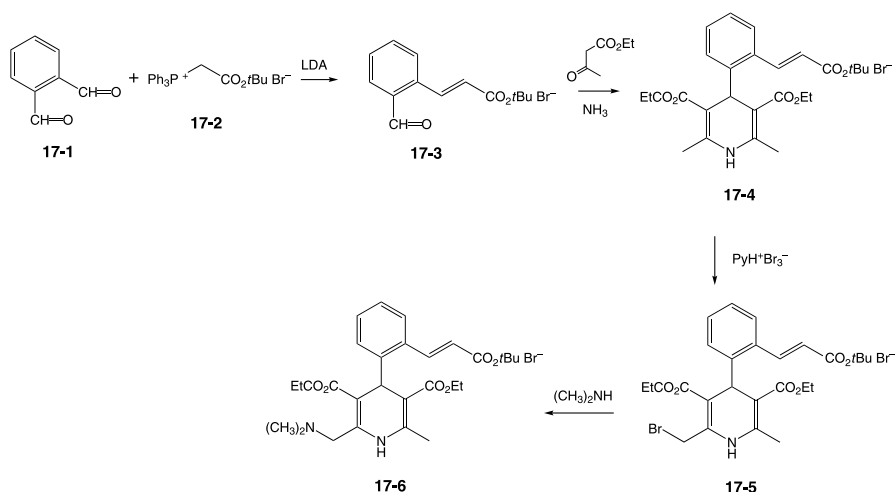
9.1.4. Piperidines

9.1.4.1. Psychotropic Compounds. The piperidines and pyrrolidines, which are so frequently found in side chains of therapeutic agents, are not usually, as noted earlier, associated with pharmacophores. Instead, they simply serve as surro-gates for open chain tertiary amines. The series of 4-aryl or -heteroaryl piperidines and piperazines that are discussed below, however, constitute an important group of clinically useful psychotropic drugs. The shared mechanism of action of this structural class, dopamine antagonism, suggests that the piperidine (or piperazine) moiety found in these compounds ring may be part of a pharmacophore.

The first agent of this class to be introduced in the clinic, **haloperidol** (**18-8**), inter-estingly shares the 4-phenylpiperidine structural fragment found in the central analge-sic agent meperidine and its derivatives (see Chapter 7). The former compound may well have been discovered in the course of further SAR studies on the opiate [20]. An unusual synthesis of **haloperidol** starts with the product (**18-1**) from Friedel–Crafts acylation of 4-fluorobenzene with succinic anhydride. Successive protection of the

ketone as its acetal by reaction with ethylene glycol, conversion of the carboxyl group to acid chloride, and finally ammonolysis gives the amide (**18-2**). This is then reduced to a primary amine (**18-3**) by means of lithium aluminum hydride. Construction of the piperidine starts with the conjugate addition of methyl acrylate to the primary amino group to give the di-ester (**18-4**). Dieckmann condensation of that intermediate leads to the formation of the β-ketoester (**18-5**) and thus cyclization. Heating that intermediate in aqueous methanol leads to hydrolysis of the keto-acid; this quickly decarboxylates to give the piperidone (**18-6**), leaving the acetal intact. Condensation with the Grignard reagent from *para*-bromochlorobenzene gives the tertiary carbinol (**18-7**). Hydrolysis with aqueous acid leads to the removal of the acetal protecting group and the formation of haloperidol (**18-8**). It was found some time after its introduction that this drug, as well as later analogues, which are widely used for the treatment of schizophrenia, are competitive inhibitors at dopamine receptor sites in the brain, diminishing the effect of the excess neurotransmitter, or receptor supersensitivity, associated with the disease. The series of often serious side effects displayed by patients on drug are likely a consequence of their dopamine antagonism.
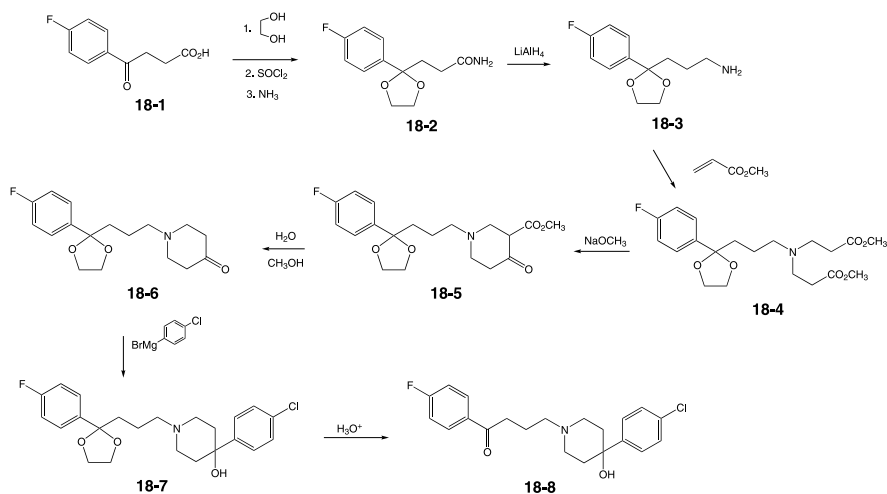
A benzimidazolone moiety replaces the aryl group on the piperidine ring in a somewhat more complex antipsychotic drug. The starting piperidone (**19-1**) for this sequence is available by a sequence analogous to that outlined for preparing (**18-5**) above; that is, Michael addition of benzylamine to ethyl acrylate followed by Dieckmann cyclization. Reaction of the product with *ortho*-phenylenediamine (**19-2**) leads directly to the imidazolone (**19-5**). This seemingly complex transform can be rationalized by assuming that the first step consists of the formation of the imine (**19-3**). The carboxylate group then migrates to nitrogen by a process analogous to the decarboxylation of β-ketoacids; the accompanying double bond rearrangement leads to the formation of the endocyclic olefin (**19-4**). An attack on the carboxylate by the adjacent amine leads to the cyclic urea with the net effect of forming unsaturated

benzimidazolone (**19-5**). Catalytic reduction over palladium leads to the loss of the benzyl protecting group and the formation of (**19-6**). A somewhat more strenuous condition leads directly to the corresponding saturated piperidine (**19-7**).
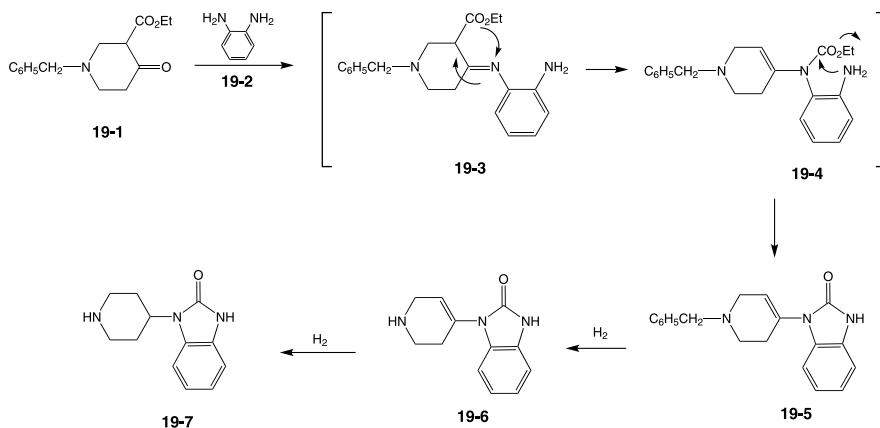
Alkylation of the basic amino group in (**19-6**) with butyrophenone (**20-1**), available from the acylation of fluorobenzene with 4-chlorobutyryl chloride, affords the antipsychotic drug **droperidol** (**20-2**) [21]. Alkylation of the fully reduced intermediate (**19-7**) with a side chain (**20-3**) yields **pimozide** (**20-4**) [22].
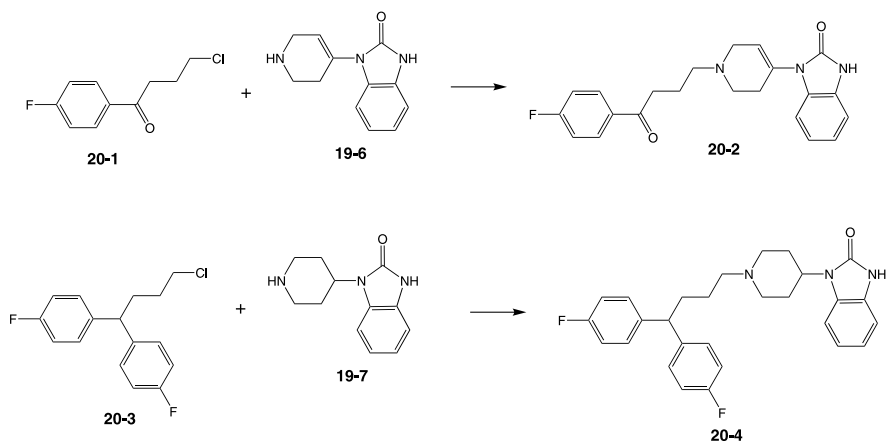
The presence of a quaternary carbon atom at the 4 position of the piperidine in the form of a spiro substituent seems to enhance potency. The starting piperidin is the product from the formal additon of cyanide and aniline to the 4 position of *N*-benzyl-4-piperidone (see Chapter 7 [**28-3**] for preparation). Reaction of that with formamide serves to form the spiro-imidazoline ring (**21-4**). The benzyl protecting group is then removed by hydrogenolysis over palladium to give the secondary

amine (**21-2**). Alkylation with 4-chlorobutyrophenone (**20-1**) affords **fluspiperone** (**21-3**). Reaction with the *bis*-fluorophenyl side chain (**20-3**) gives **fluspiriline** (**21-4**) [23].
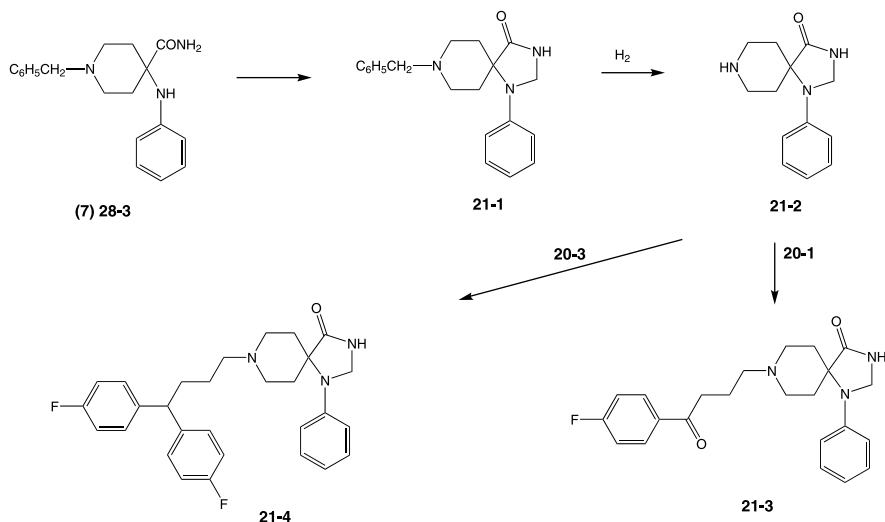
Yet another piperidine-based antipsychotic agent replaces the butyrophenone or diarylpropyl function found in earlier compounds by a benzopyrimidine group. The synthesis starts by the conversion of the carboxylic acid in piperidine (**22-1**) to its acid chloride. Reaction with 1,3-difluorobenzene (**22-2**) in the presence of aluminum chloride affords the acylated product (**22-3**). Reaction with hydroxylamine leads to the corresponding oxime (**22-4**). Treatment of that derivative with a base
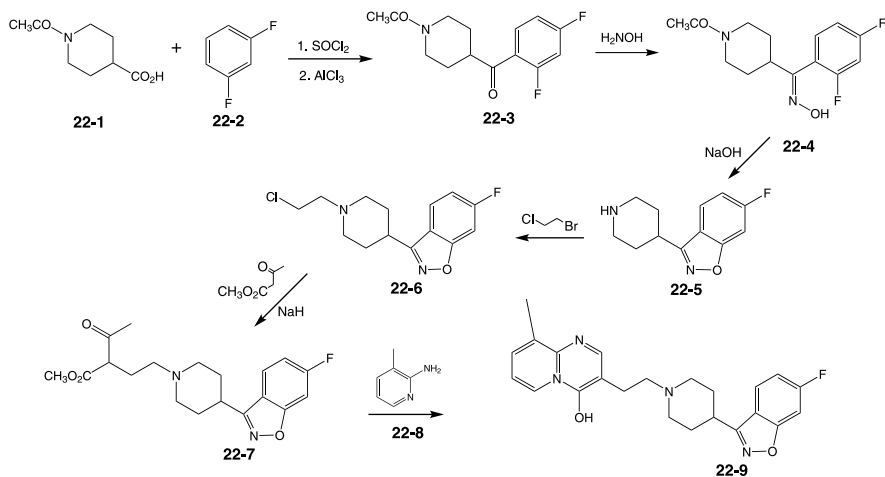
leads to the displacement of the ring fluorine by the alkoxide from the adjacent oxime group to form an isoxazole ring; the acyl protecting group on piperidine nitrogen is removed in the process to afford the free amine (**22-5**). That function is then alkylated with 2-chloroethylbromide to add the short side chain (**22-6**). Reaction of that with the carbanion from methyl acetoacetate and a base leads to the displacement of the remaining halogen on the side chain to afford the alkylated derivative (**22-7**). Condensation of this product with 3-methyl-2-aminopyridine (**22-8**) leads to the formation of the fused pyrimidine and thus **ocaperidone** (**22-9**) [24].

9.1.4.2. Miscellaneous Piperidines.

Secretion of saliva is among the many functions controlled by the cholinergic nervous systems—this accounts for the dry mouth caused by anticholinergic drugs. A bicyclic piperidine that acts as a cholinergic agonist has proven useful for stimulating the production of saliva in patients who suffer from dry mouth syndrome. The starting material, piperidine (**23-1**), for the enantioselective synthesis of **civemeline** (**23-9**) is available in a few steps from piperidine carboxylic acid. The secondary amino group is first protected as its *tert*-butoxycarbonyl derivative by reaction with the corresponding anhydride. The carbonyl group is then converted to a methylene group by reaction with the ylide from triphenylmethyl phosphoium bromide (**23-2**). Oxidation of the newly introduced olefin under Sharpless conditions in the presence of L-tartrate then
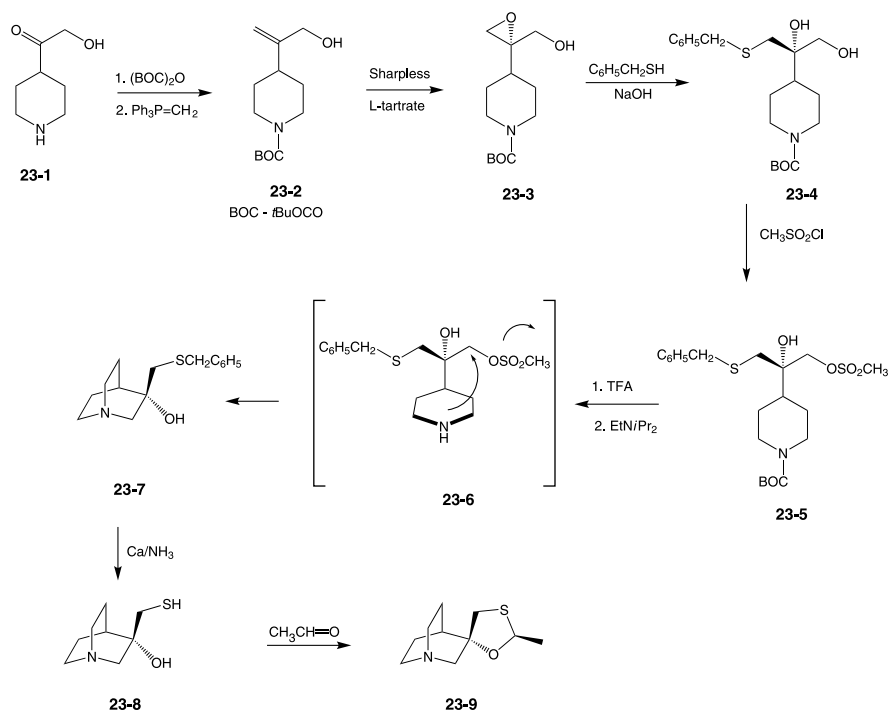
affords chiral epoxide (**23-3**) as a single enantiomer. The anion from benzylthiol and base then opens the epoxide by an attack on the terminal carbon in the oxirane; the product (**23-4**) retains its steric identity since the point of attack is not itself chiral. The hydroxyl group is next converted to a good leaving group by reaction with methanesulfonyl chloride. Treatment of that product (**23-5**) with trifluoroacetic acid results in the cleavage of the protective group on nitrogen to afford the secondary amine (**23-6**). That product is next exposed *in situ* to a base. The basic piperidine nitrogen then displaces the methanesulfonate group across the ring to form the bridged bicyclic quinuclidine (**23-7**). The benzyl protecting group on sulfur is then removed by a variant on the Birch reduction: treatment with calcium in liquid ammonia yields hydroxythiol (**23-8**) as the pure *S* enantiomer. Reaction of this last product with acetaldehyde gives the corresponding thioacetal (**23-9**) and thus cevimeline [25]. This last reaction results in the formation of the new chiral center as a single enantiomer probably due to steric induction from the adjacent chiral center.

The side effects of the classic agents for treating epilepsy, such as the hydantoins, have encouraged the search for agents that act by more specific mechanisms. Antagonists of the re-uptake of the neurotransmitter gamma-aminobutyric acid (GABA) have shown promise as alternative agents for treating epilepsy. A number of approaches are likely possible for preparing the starting *bis*-thiophenyl ketone (**24-1**) such as, for example, the addition of a thiophene lihium reagent to a thiophene carboxylate. Reaction of the ketone with the Grignard reagent from cyclopropyl bromide yields the tertiary alcohol (**24-2**). Hydrogen bromide then causes that group to undergo the cyclopropylcarbinyl-homoallyl rearrangement to form the allyl bromide (**24-3**). The allylic halogen is readily displaced by chiral ethyl nipecotate (**24-4**). There is thus obtained **tiagabine** (**24-5**) as the *S* enantiomer [26].
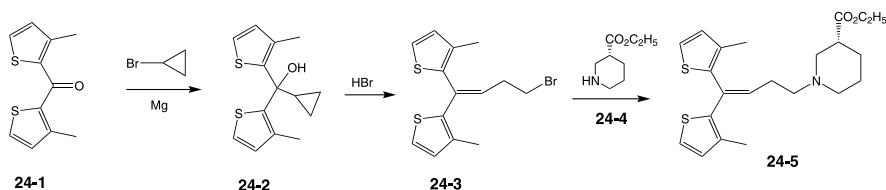
9.1.5. Pyridones and Glutarimides

A decrease in the force of contraction of the heart muscle is one of the symptoms that marks heart failure. Digitoxin and related steroid glycosides constitute one of the oldest and until quite recently most effective means of increasing cardiac contractile force. These drugs do, however, show a very narrow therapeutic index and thus require careful patient monitoring. The science of pharmacokinetics may have owed its origin at least in part to the need for monitoring blood levels of these drugs. The two pyridones that follow show clinically useful cardiotonic activity on oral administration without the narrow therapeutic activity of the steroidal cardiac glycosides. A much larger series of pyrazinones that show the same activity is discussed later in this chapter.

Reaction of pyridyl-4-acetaldehyde (**25-1**) with DMF acetal gives the product corresponding to the aminoformyl derivative (**25-2**). The first step in the reaction of that intermediate with the anion from cyanoacetamide can be envisaged as involving the replacement of the dimethylamino group to form (**25-3**), probably by an addition-elimination sequence. Imine formation of amide nitrogen with the formyl group will then lead to the cyclization and formation of the pyridone ring in (**25-4**). Hydrolysis with a strong acid then gives the corresponding amide (**25-5**). Treatment of this last intermediate with bromine in the presence of a base leads to a classical Hofmann rearrangement of the amide to an amine with loss of the carbonyl carbon. There is thus obtained the cardiotonic drug **amrinone** (**25-6**) [27].
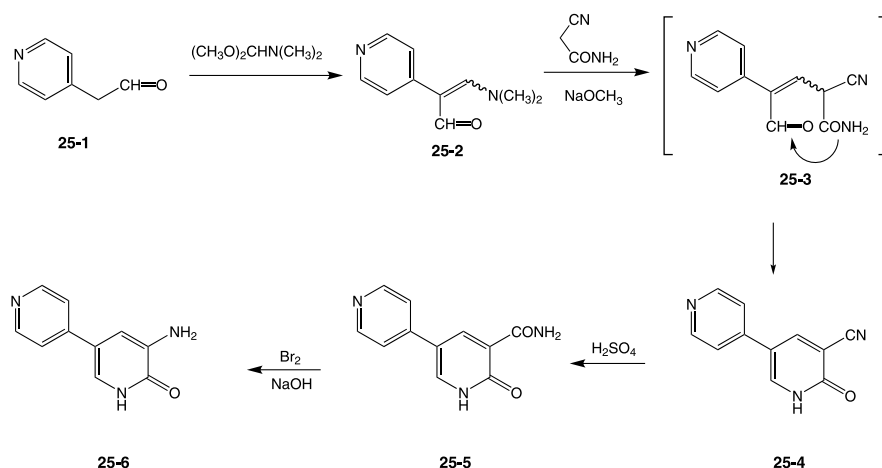
An analogous scheme is used for the synthesis of the cardiotonic agent **milrinone** [28]. The key aminoformyl derivative (**26-2**) is obtained in this case by condensation of 4-pyridylacetone (**26-1**) with DMF acetal. Reaction with cyanoacetamide in the presence of a strong base proceeds exactly as above to give the pyridone (**26-3**) by a parallel set of transformations. Note that the nitrile is left as such in this drug.
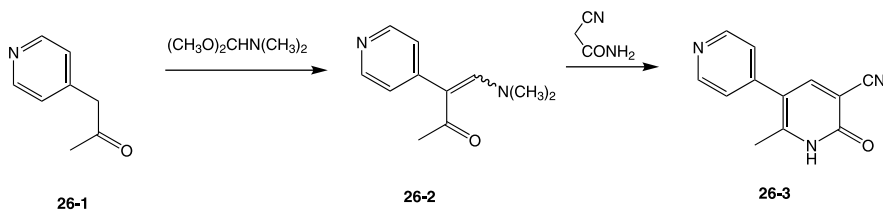
The utility of barbituric acid derivatives as sedative-hypnotic agents is discussed in more detail later in this chapter. Studies on the chemical simplification of these pyrimidinetrione derivatives led to the discovery that pyridinediones, or glutarimides,

also acted as sedative-hypnotic agents. The synthesis of the parent compound in this series, **gluthethimide (27-3)**, starts with the conjugate addition of the product (**27-1**) from ethylation of phenylacetonitrile with ethyl acrylate to give the cyano-ester (**27-2**). Heating that product in acetic acid leads to the formation of the glutar-imide, **glutethimide (27-3)** [29], probably via an initial hydrolysis of the nitrile to an amide. Prior nitration of the acetonitrile gives the analogue (**27-4**). This yields the nitro glutarimide (**27-5**) when subjected to the two-step sequence. Reduction of the nitro group by catalytic reduction affords **aminoglutethimide (27-6)** [30].
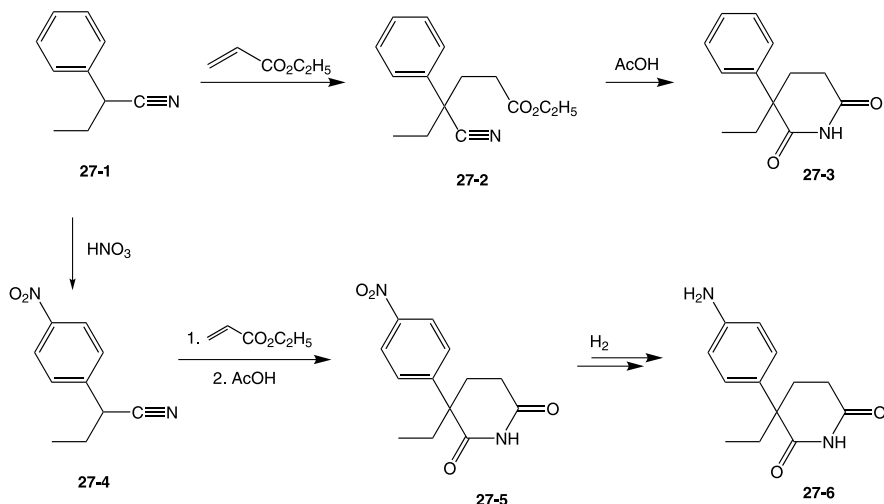
Steroid aromatase enzyme catalyzes an essential step in the endogenous synthesis of estrogens. The aromatase inhibiting activity of **aminoglutethimide**, which was discovered quite adventiously in the clinic, led to some use of this drug in the treat-ment of breast cancer. The very modest enzyme inhibiting activity displayed by the drug led to a search for more potent analogues. The derivative in which a pyridyl group replaces the aniline moiety was designed specifically as an aromatase inhibitor. The synthesis of this agent, which is analogous to those described above, involves the conjugate addition of the ester (**28-1**) to acrylamide to give the ester-amide (**28-2**). Treatment of that intermediate with sodium ethoxide leads to imide formation to give **rogletimide (28-3)** [31].
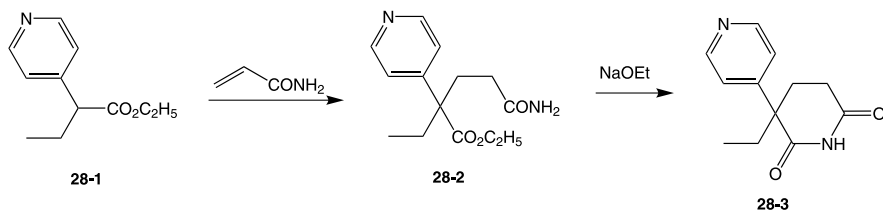
No biologically active compound has arguably had quite the effect on the governmental regulations that affect the pharmaceutical industry as has **thalidomide (29-4)**. The profound malformations caused in offspring of women taking this nonbarbiturate sedative caused reappraisal of government oversight of pharmaceuticals in most of Western Europe. In the United States, the event provided the final push for a major revision of the Food and Drug Laws that govern the FDA. The low-level research that continued on this drug, in spite of its ill repute, unexpectedly showed that the compound affected immune function. It was found that only one enantiomer causes fetal malformations, though both are sedatives. The drug was, for example, recently approved by the FDA for the treatment of complications from leprosy. It has in addition been investigated as an adjunct for treating some malignancies. The compound itself was in fact prepared in quite a straightforward manner by reaction of the phthalimide (**29-3**) of *RS* glutamic acid (**29-2**) with ammonia.
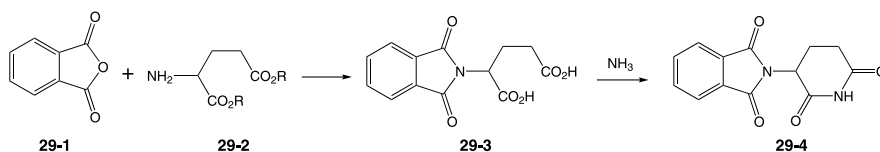
Further research on related compounds revealed a series of analogues that inhibit tumor necrosis factor (TNF-α). Synthesis of the aminosuccinimide moiety starts by cyclization of carbobenzyloxy glutamine (**30-1**) by treatment with carbonyl diimidazole. Catalytic hydrogenation of the product removes the protecting group to afford the free amine (**30-2**). The aromatic moiety of the target compound is prepared by free radical bromination of the methyl group in the benzoic acid (**30-3**) to give the bromomethyl derivative (**30-4**). Condensation of this last with the succinimide (**30-2**) leads to isoindolone (**30-5**). A second hydrogenation step reduces the nitro group to an aniline to afford **lenalidomide (30-6)** [32].
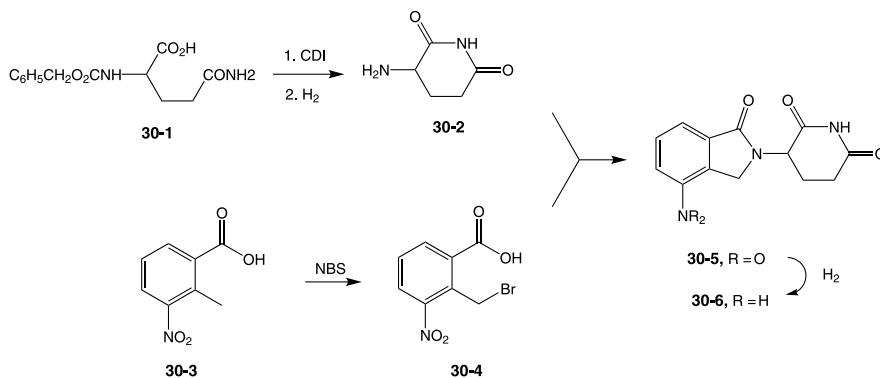
Moving one of the carbonyl groups away from the amide function of course markedly reduces the acidity of the proton on nitrogen. It is interesting that

sedative-hypnotic activity is retained in the face of this change. The synthesis of this agent, **methyprylon (31-6)**, starts with the formylation of the doubly ethylated acetoacetate **(31-1)** by means of ethyl formate and sodium ethoxide to give **(31-2)**. Reaction of the formyl derivative, shown as the hydroxymethyl tautomer with ammonia, converts the product to its eneamine **(31-3)**; this cyclizes to the piperidine-dione **(31-4)** on heating. Treatment of the product with formaldehyde in the presence of sodium bisulfite leads to the carbinol **(31-5)** by aldol condensation. Catalytic reduction leads first to the loss of the allylic hydroxyl by hydrogenolysis; reduction of the ring double bond then gives **methyprylon (31-6)** [33].
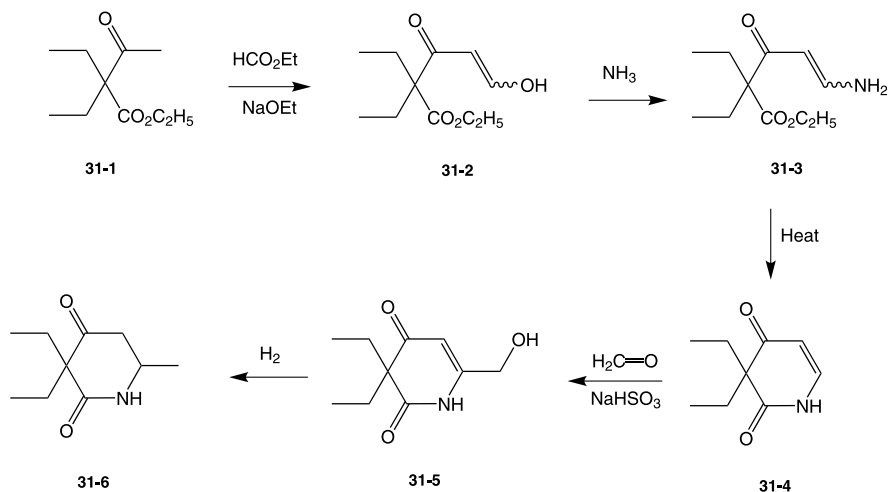
9.2. RINGS THAT CONTAIN TWO HETEROATOMS

9.2.1. Pyridazines

One approach to the treatment of hypertension comprises overcoming the vascular resistance due to contracted arterioles by use of vasodilators. The structures of such agents quite frequently incorporate the elements of an amidine or guanidine function. The preparation of the antihypertensive agent **hydracarbazine (32-6)**, which may be viewed as containing an embedded amidine, starts with the reaction of keto-acid **(32-1)** with hydrazine. The sequential formation of a hydrazide and hydrazone, though not necessarily in that order, leads to the pyridazinone **(32-2)**. Treatment of that product with bromine in acetic acid results in the introduction of a double bond and the formation of the derivative **(32-3)**, which has an aromatic char-acter. The chemically inert nature of the ring is illustrated by the fact that exposure to potassium dichromate leads to the oxidation of the ring methyl group to a carboxylic acid and thus the formation of **(32-4)**. That function is next converted to the corre-sponding ester by treatment with ethanolic acid. In a standard reaction of heterocyclic

enols, the ring hydroxyl is next replaced by chlorine by means of phosphorus oxychloride. The displacement of chlorine from the thus-obtained intermediate (**32-5**) by hydrazine followed by treatment with ammonia to form the amide yields **hydracarbazine** (**32-6**) [34].
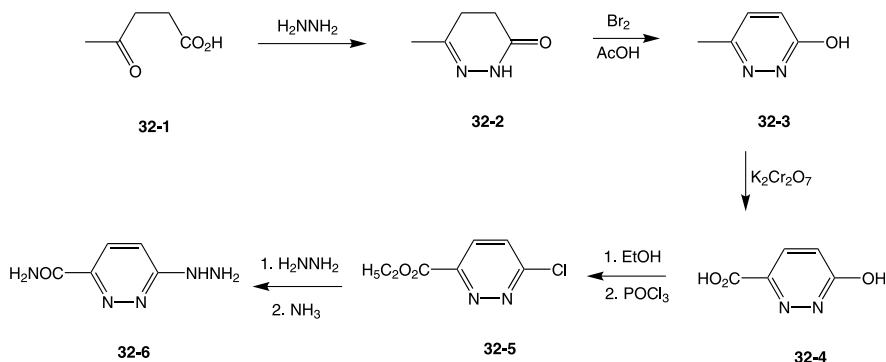
The side effects that accompany the use of vasodilators, such as fluid retention and increased heart rate, may be due to sympathetic reflex effects; they can be diminished by co-administration of β-blockers. The antihypertensive agent **prizidilol** (**33-5**) may be viewed as an analogue of **hydracarbazine**, with a built-in β-blocker moiety. The key chloropyridazine (**33-2**) is prepared by a sequence quite analogous to that above, involving the formation of the pyridazinone ring followed by dehydrogenation to (**33-2**), shown as its keto tautomer. Treatment with phosphorus oxychloride then gives (**33-3**). The oxypropanolamine side chain is then built onto the phenol function in that compound by the standard scheme (epichlorohydrin followed by *tert*-butylamine) discussed in detail in Chapter 2 (**33-4**). The displacement of chlorine by hydrazine then gives prizidilol (**33-5**) [35].
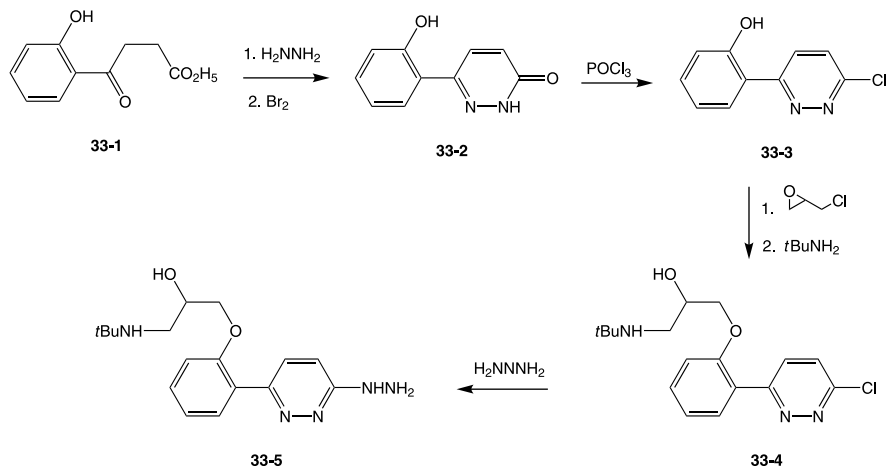
The structure of the pyridazine-based antidepressant agent **minaprine** (**34-6**) departs markedly from both the older tricyclic drugs and the more recent selective serotonin re-uptake inhibitors. There is evidence that the compound acts via a dopa-mimetic route. Friedel-Crafts acylation of benzene with itaconic anhydride (**34-1**) leads to the keto-acid (**34-2**). Condensation with hydrazine leads to the formation of the hydrazine and hydrazide bonds; the double bond shifts into the ring to give the fully unsaturated pyridazinone (**34-3**); this is then converted to the chloride (**34-4**) in the usual way. The displacement of halogen by the amine on 3-(*N*-morpho-lino)propylamine (**34-5**) affords (**34-6**) [36].
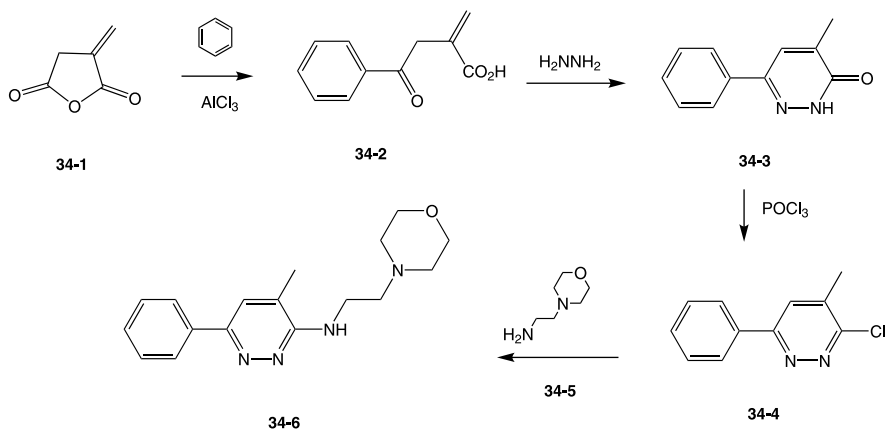
The role of the pyridone ring as a pharmacophore in cardiotonic agents such as **amrinone** (**25-6**) has been noted earlier; very analogous activity is obtained with compounds in which the heterocyclic ring is replaced by a pyridazinone. The synthesis of the first of these agents, **pimobendan** (**35-6**), starts with the acylation of the amino group in nitro-aniline (**35-2**) with anisoyl chloride (**35-1**) to give amide (**35-3**).
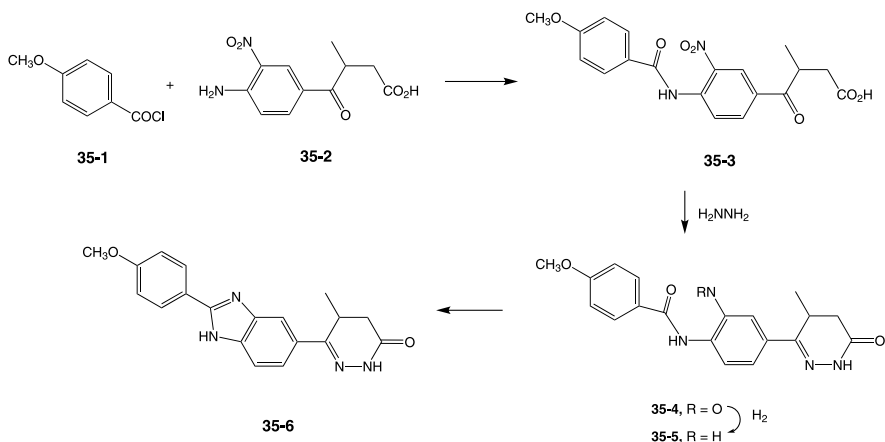
The keto-acid function is then converted to a pyridazinone by treatment with hydrazine (**35-4**). Catalytic hydrogenation then converts the nitro group to an amine (**35-5**); cyclization of the resulting *ortho* amino amide by means of a strong acid leads to the formation of the corresponding benzimidazole. There is thus obtained **pimobendan** (**35-6**) [37].

The quinazolinone moiety (**36-3**) for the cardiotonic agent **prindoxan** (**36-5**) is formed by reaction of diamine (**36-1**) with carbonyl diimidazole (**36-2**). Friedel-Crafts acylation of the product with the half-acid chloride from methyl succinate gives the corresponding keto-ester (**36-4**). The pyridazinone (**36-5**) is then obtained by condensation of that product with hydrazine [38].
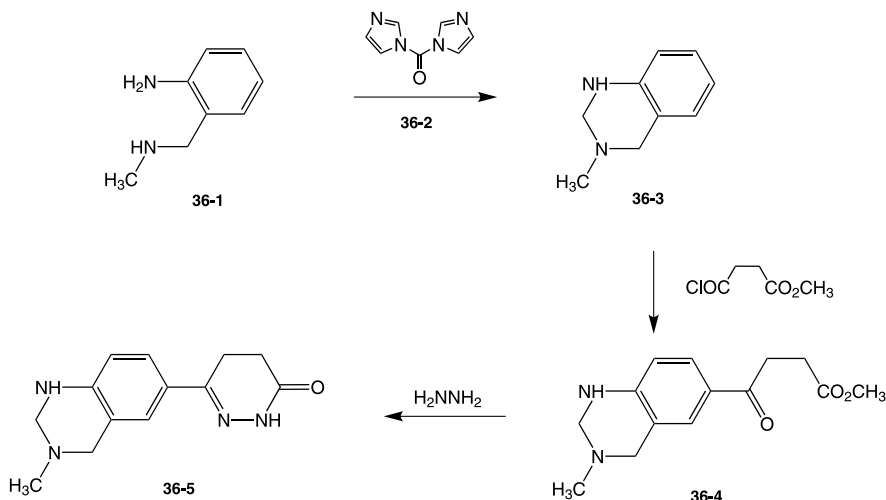
9.2.2. Pyrimidines

9.2.2.1. Antibacterial Agents. The era of modern antibiotics relies largely on metabolic differences between pro- and eukariotic species. The selective toxicity of sulfonamides, for example, as noted in Chapter 2, is due largely to the fact that bacteria obtain folates by *de novo* synthesis while mammals obtain those compounds from their diet. Folic acid (**37-1**), in fact, needs further transformation to give the active compound. The activation requires the conversion of the pyrazine ring in (**37-1**) to folinic acid to its tetrahydro derivative by two sequential reductions catalyzed by the enzyme dihydrofolate reductase (DHFR). A series of pyrimidine-based antibiotics depend on the fact that these compounds show preferential binding to the bacterial over mammalian DHFR. These agents consequently show selective toxicity against bacteria. The pyrimidine ring in these drugs presumably mimics the corresponding fused pyrimidine ring in folic, and dihydrofolic acid.
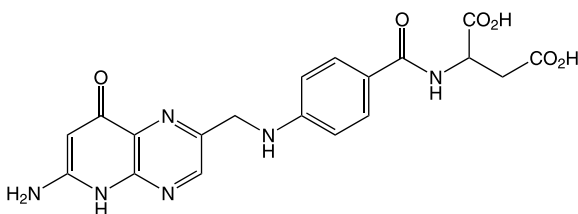
37-1

Base-catalyzed condensation of 4-chlorophenylacetonitrile (**38-1**) with ethyl propionate leads to the corresponding acylated derivative, shown as its enol tautomer (**38-2**). Reaction of that intermediate with diazomethane, a reagent not likely to be used in commercial production, leads to the enol ether (**38-3**). Construction of the pyrimidine ring then involves a fairly standard scheme that consists of condensation of a 1,3 dicarbonyl component, or its equivalent, with an amidine-containing moiety. In the case at hand, the reaction of (**38-3**) with guanidine can be visualized as proceeding to a transient intermediate such as (**38-4**) by addition-elimination of one of the basic amino groups to the enol ether. The addition of the primary amine in the adduct to the nitrile will lead to cyclization. Bond rearrangement to give the fully conjugated isomer leads to the antibacterial agent **pyrimethamine** (**38-5**) [39]. The somewhat selective toxicity to cancer cells of many antineoplastic drugs depends on the faster rate of growth of those cells. Antimetabolites have thus been intensively investigated for that application. The folate reductase antagonist **etoprine** (**38-6**), prepared by an analogous route, has been investigated clinically because of its appreciable activity against the mammalian enzymes.

38-1

38-2

38-3

38-4

38-5, X = H

38-6, X = Cl
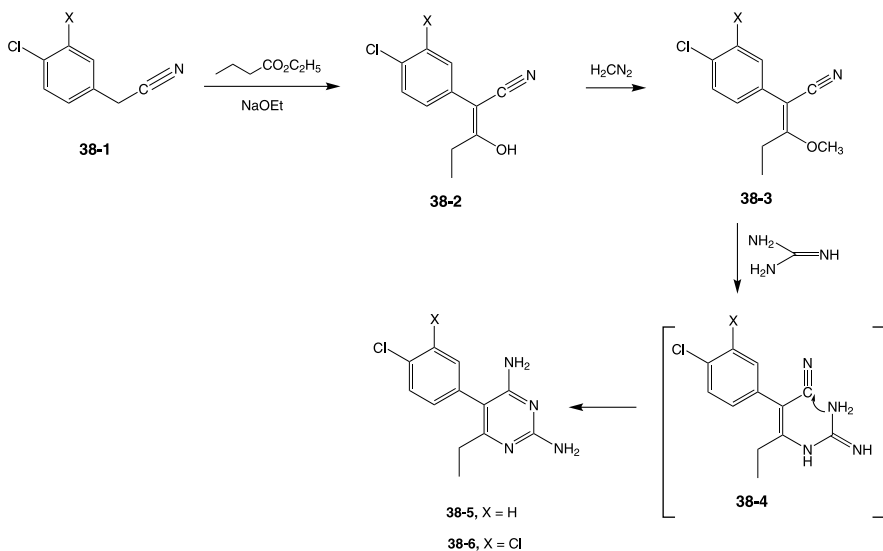
Interposition of a methylene group between the two rings leads to agents that show somewhat higher selectivity for bacterial enzymes. The preparation of the still widely used DHFR antagonist **trimethoprim** (**39-5**) starts by condensation of trimethoxy-benzaldehyde (**39-1**) with 3-ethoxypropionitrile. The first step in the reaction with guanidine probably involves the replacement of the allylic ethoxy group in (**39-2**) by guanidine nitrogen to give an intermediate such as (**39-3**). This then undergoes the usual cylcization reaction (**39-4**) and bond reorganization to give **trimethoprim** (**39-5**) [40]. This compound finds extensive use in fixed combinations with the sulfonamides achieving improved antibacterial efficacy by inhibiting the sequential steps in the synthesis of folates.
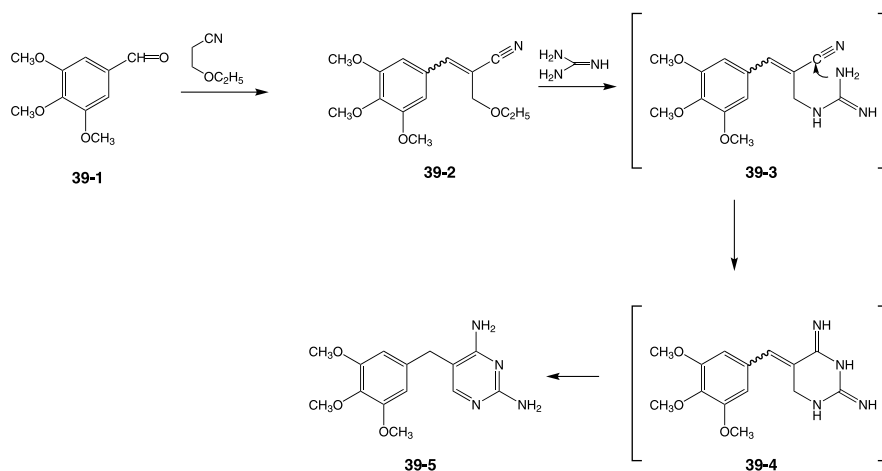
A somewhat different route is used to prepare an analogue that bears additional oxygen. The sequence, in this case, starts by base-catalyzed formylation of the hydro-cinnamic acid derivative (**40-1**) with ethyl formate. Condensation of the product (**40-2**) with guanidine in this case leads to a pyrimidone (**40-3**), with the cyclization involving an ester-amide interchange between guanidine and the ester. Reaction of
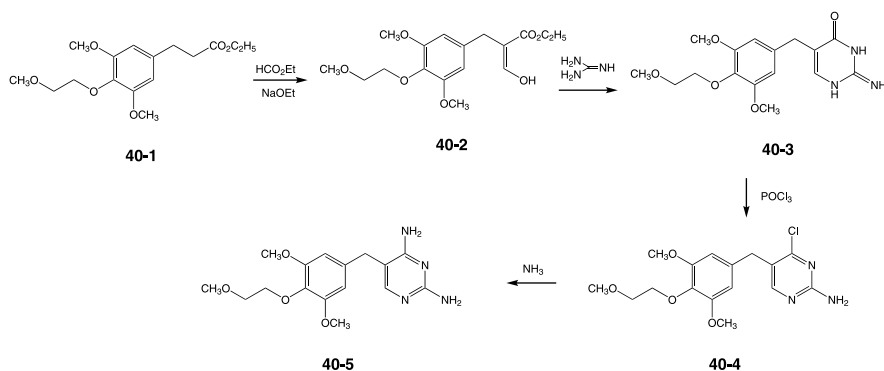
(**40-3**) with phosphorus oxychloride leads to the formation of the chlorinated derivative (**40-4**). The displacement of halogen by ammonia gives the antibacterial compound **tetroxoprim** (**40-5**) [41].

A very potent, more recently introduced, example has shown promise for treating infections by antibiotic-resistant bacteria. The synthesis of a fragment necessary for building a fused ring begins with aluminum chloride catalyzed acylation of *bis*-sylilated acetylene (**41-1**) with carboxycyclopropyl chloride. The reaction interestingly stops with the introduction of a single acyl function (**41-2**). The newly introduced ketone is then reduced to the corresponding alcohol (**41-3**) with sodium borohydride. Mitsonobu reaction of this alcohol with the phenol (**41-4**) leads to the alkylation product, ether (**41-5**). This product undergoes internal $2 + 4$ electrocyclic addition on heating to form a dihydropyran ring and thus the product (**41-6**). The ester grouping is then subjected to a reduction-back oxidation sequence in order to convert the ester group to the corresponding aldehyde (**41-7**). Aldol condensation of that carbonyl function with the 3-anilidopropionitrile probably proceeds initially to the adduct (**41-8**). The double bond then shifts out of conjugation with the aromatic ring to give (**41-9**) as the observed product. The reaction of that intermediate with guanidine can be viewed for bookkeeping purposes as involving the addition of one of the guanidine nitrogens to the nitrile while another displaces the anilide by an addition-elimination step to close the pyrimidine ring. There is thus obtained the antibacterial agent **iclaprim** (**41-10**) [42].
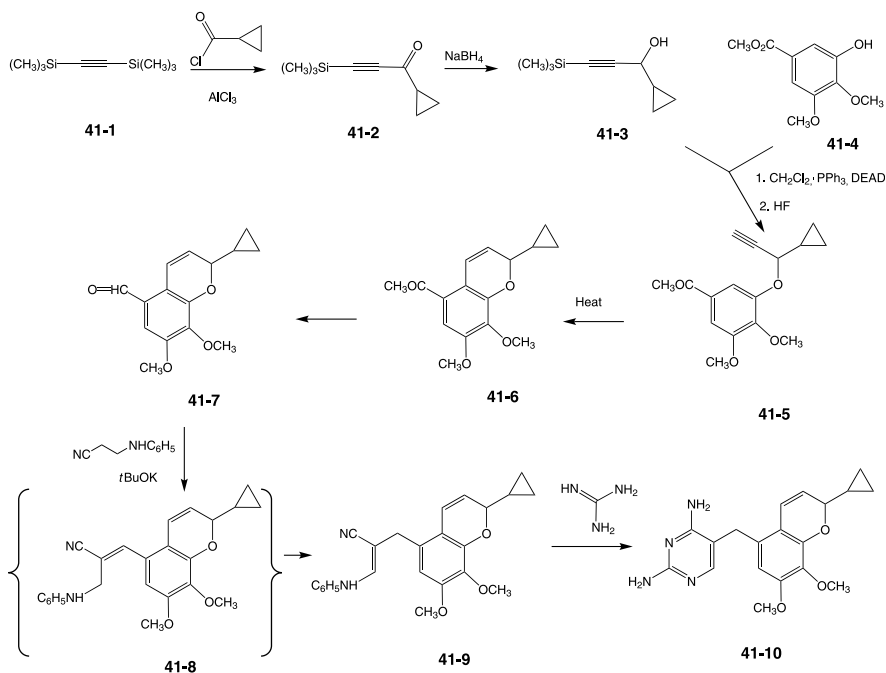
A compound that includes an aminopyrimidine ring as well as the quaternary salt present in thiamine shows preferential inhibition of absorption of that co-factor by *coccidia* parasites over uptake by vertebrates. The compound is thus used in poultry where coccidiosis is an economically important disease. Condensation of ethoxymethylenemalononitrile (**42-1**) with the amidine (**42-2**) leads to the aminopyrimidine (**42-4**), probably via the intermediate addition-elimination intermediate (**42-3**). The nitrile group is then reduced to the methylamino derivative (**42-5**) by means of lithium aluminum hydride. Exhaustive methylation, for example by reaction with formaldehyde and formic acid, followed by methyl iodide leads to the quaternary methiodide (**42-6**). The quaternary salt is then displaced by bromine, and the resulting benzylic-like cylic halide (**42-7**) is displaced by 2-picoline (**42-8**). There is thus obtained **amprolium** (**42-9**) [43].
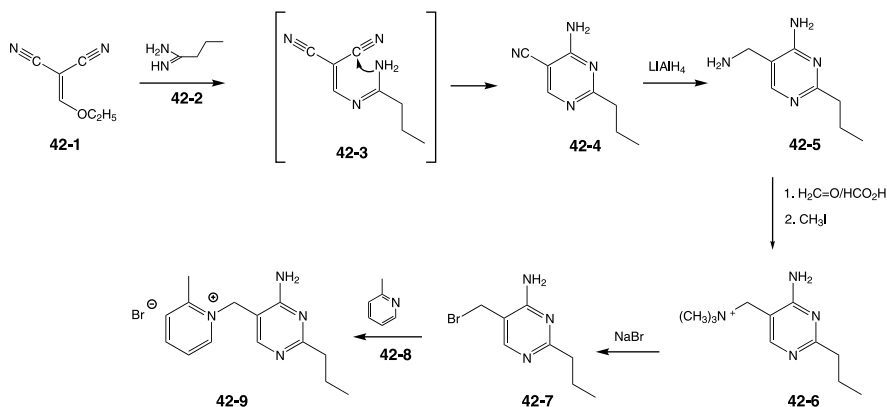
9.2.2.2. Antiviral and Antineoplastic Pyrimidines

9.2.2.2.1. Nucleosides. Viruses differ from bacteria and fungi in a most fundamental way in that they are not able to reproduce independently. A virion in essence consists of a chain of DNA, or RNA in the case of a retrovirus, packaged with a small group of specialized proteins. The virus actually replicates by taking over the infected cells' reproductive apparatus, in effect causing the cell to synthesize new virions. Chemotherapy of viral disease must thus rely on very subtle biochemical differences between normal and infected cells instead of the large divergences in biochemistry between microbial and host cells that provide the basis of antibiotics. The somewhat looser discriminatory power of the enzymes in viral cells for the nucleotides involved in replication has made it possible to identify a number of closely related false substrates, The resulting antagonists have provided the bulk of today's antiviral agents; additional compounds are discussed in the section on triazines, which follows later in this chapter, and that on purine nucleosides in Chapter 12.

The nuleotide, uridine (**43-1**), provides the starting material for one of these agents. Treatment of that compound with mercuric chloride leads to the mercuration

of the pyrimidine ring to afford (**43-2**). Reaction of this organometallic derivative with ethylene in the presence of a platinum salt leads to the alkylated product (**43-2**). Catalytic hydrogenation of the double bond then affords the antiviral compound **edoxudine** (**43-4**) [44].
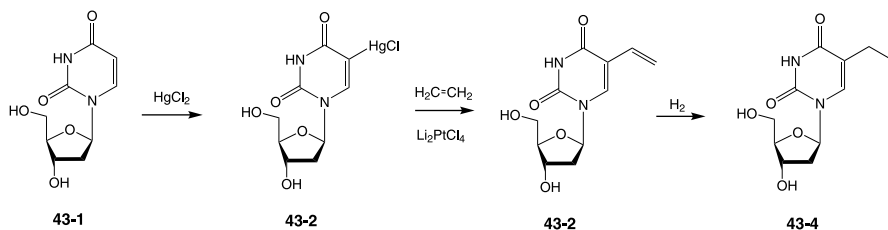
Similar chemistry is used to prepare the antiviral agent **sorivudine** (**43-5**); this compound is also endowed with an unnatural sugar in the arabinose configuration. The side chain is attached as above by the chloromeruration of uracyl arabinoside (**44-1**). Reaction of the organometallic (**44-2**) with ethyl acrylate leads to the coupling product (**44-3**). The ester grouping is then saponified to yield the corresponding acid (**44-4**). Treating the acid with *N*-bromosuccinimide leads to a Borodin-like replacement of the carboxyl group by bromine. The resulting reactive allylic halogen in the product, sorivudine (**43-5**) [45], may play a role in the compound's activity against the herpes virus.
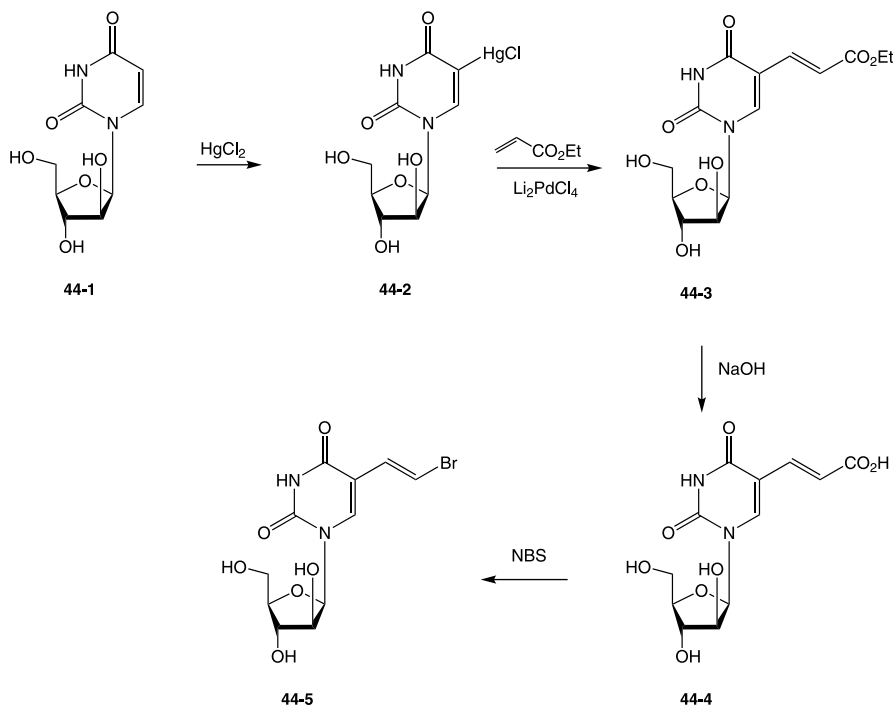
A small series of unusual viruses, most notably the human immunodeficiency virus (HIV), the cause of AIDS, incorporate an RNA rather than a DNA chain. The first step in viral replication, after the virion has gained entry to the cell's nucleus, thus involves the translation of the genome into DNA by an enzyme designated reverse transcriptase. The transcriptase proper regulates the more common translation of DNA to RNA that precedes protein synthesis. The reverse enzyme has proven a fruitful source for anti-HIV drugs, many of which comprise modified nucleosides. The synthesis of the first anti-HIV drug to reach the clinic, **zidovudine** (**45-3**), more familiarly known as AZT, starts with the reaction of thymidine (**45-1**), shown as the enol tautomer, with the powerful dehydrating agent diethylaminosulfur tertafluoride (DAST). The stereochemistry of the resulting cyclic ether (**45-2**) strongly suggests that the initial step involves the transformation of the sugar hydroxyl to a good leaving group. This is then displaced by the pyrimidine enol with consequent inversion. Treatment of the intermediate with sodium azide leads to a ring opening and a second inversion step; there is thus obtained the reverse transcriptase inhibitor **zidovudine** (**45-3**) [46].

| 45-1 | 45-2 | 45-1 |
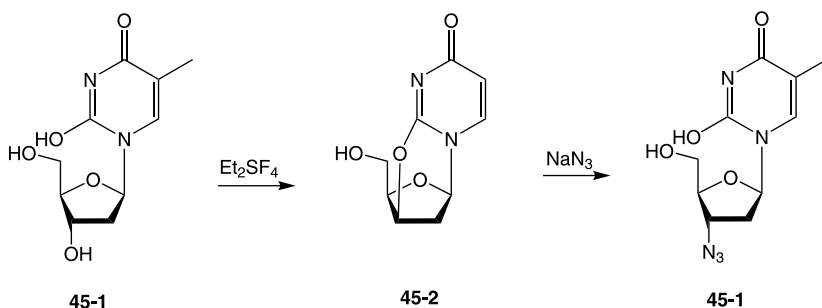
Nucleosides that incorporate unusual substitutents can also show cytotoxic activity in higher organisms by a mechanism analogous to that which leads to antiviral activity. Such compounds have been investigated as antineoplastic agents in the expectation that they would be selectively cytotoxic in the quickly dividing and less regulated cancer cells. Thus, inversion of the hydroxyl group to the $2'\alpha$ position of cytidine (**46-1**) leads to the anticancer drug cytosine arabinsoside, **cytarabine** (**46-2**). Replacement of both protons at the 2 position by fluorine similarly leads to an antineoplastic agent. It was found several decades ago that the conversion of pyrimidne bases to their silyl ethers enhanced the reactivity of ring nitrogen. Thus, exposure of the *bis*-silyl ether (**46-3**) from 4-aminopyrimidine-2-one to the anomeric mesylate from the protected fluorosugar (**46-4**) leads to the formation of (**46-5**) as a 1:1 mixture of anomers. The benzyl protecting groups are then removed by catalytic hydrogenation; separation of the compound that corresponds to the anomer with the natural β configuration affords **gemcitabine** (**46-6**) [47].

46-1 **46-2**

46-3 **46-4** **46-5** **46-6**
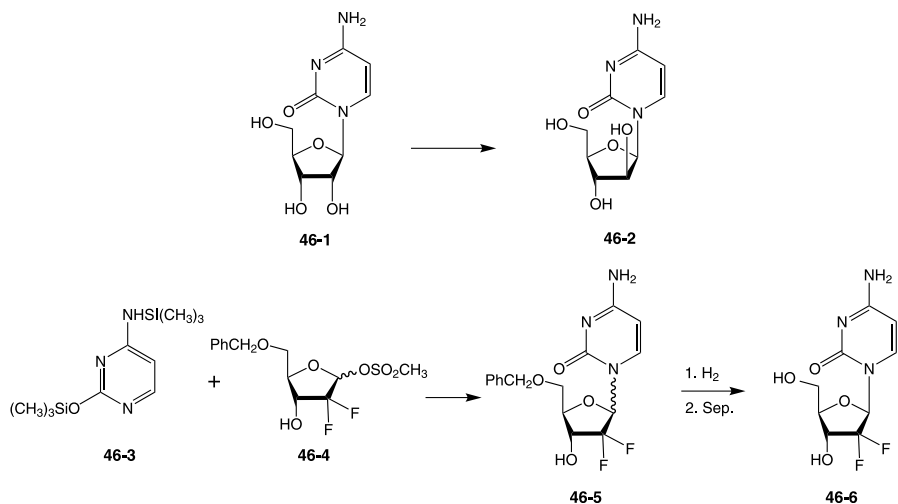
Interposing a methyne group between the sugar and the fluorine-bearing atom leads to **tezacytabine** (**47-8**), a compound that showed significant antitumor activity in a variety of model systems. This activity did not, however, hold up in the clinic, resulting in the discontinuation of further clinical trials. Reaction of cytidine (**46-1**) with the *bis*-chloro tetraisopropylsiloxane (**47-1**) results in a reaction with the hydroxyl groups at positions 3 and 5 of the sugar, forming a bridged structure in which the oxygen atoms at those positions are protected (**47-2**). The difunctional

46-1 **47-1** **47-2** **47-3**

47-7 **47-6** **47-5**
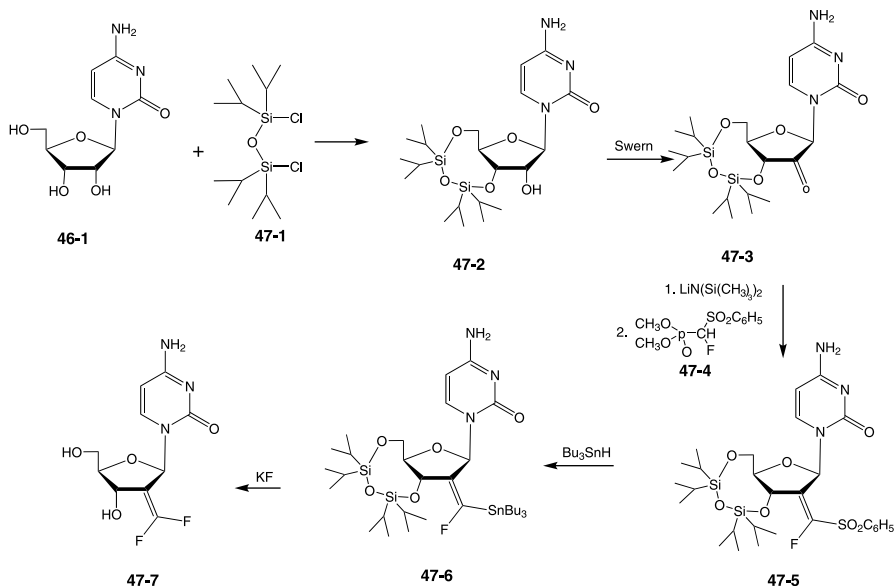
reagent is apparently too long to form the more common 2,3 cyclic protected derivative. Oxidation by means of oxalyl chloride in dimethyl formamide then gives the ketone (**47-3**). That function is then condensed with the ylide from the complex phosphonate (**47-4**) to afford the substituted exomethylene derivative (**47-5**). Reaction of that with tributyl tin hydride results in the replacement of the phenyl sulfone by tributyl tin (**47-6**). Treatment of this last product with potassium fluoride results in the cleavage of the silicon-oxygen bonds as well as the replacement of tin by hydrogen. This leads to the antimetabolite tezacitabine (**47-7**) [48].

The 2′,3′-dideoxy derivative of cytidine, DDC, also shows clinical anti-HIV activity. The synthesis starts by conversion of deoxycytidine (**45-1**) to its *bis*-methanesulfonate ester (**48-1**). Reaction of that mesylate with sodium hydroxide leads to the fused oxetane ether (**48-3**). This reaction consists formally of the hydrolysis of the 5′ mesylate to an alcohol followed by backside displacement of the 4′-mesylate. Evidence suggests, however, that the first step involves the formation of a bridged cyclic ether such as (**48-2**); addition of hydroxide to the imine system would result in breaking the bridge bond; the resulting alkoxide would then displace the adjacent mesylate to form (**48-3**). Reaction of that product with a strong base leads to a ring opening of the fused ring and the formation of the double bond (**48-4**). Catalytic hydrogenation completes the synthesis of the reverse transcriptase inhibitor **zalcitabine** (**48-5**) [49].
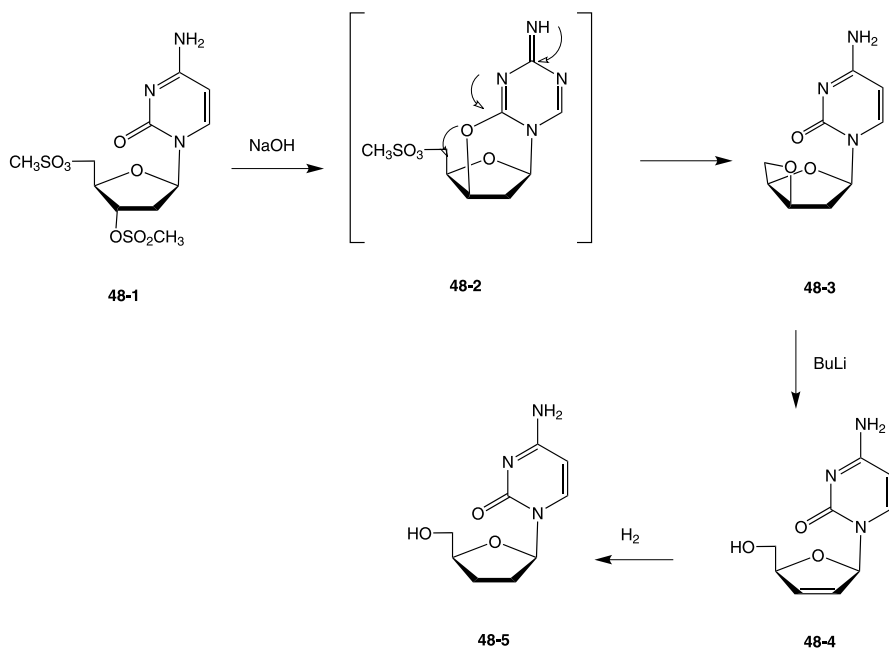
A significantly different strategy is used in the preparation of the corresponding uridine derivative that retains a double bond in the sugar-like moiety. One of the

syntheses for such derivatives begins by protection of the hydroxyl in chiral hydroxybutyrolactone (**49-1**) by reaction with *bis*(*tert*-butyldimethylsilane) to afford the silyl ether (**49-2**). Treatment of that intermediate with hexamethyldisilazane and lithium leads to the silyl-enol ether (**49-3**). This is turn allowed to react with phenylselenyl bromide. Selenium adds to the enol restoring the ketone; the selenated derivative is obtained as a mixture of diastereomers in which the transoid epimer (**49-4**) predominates. The carbonyl group is then reduced by means of diisobutylaluminum hydride and the resulting carbinol is converted to its acetate as a mixture of anomers (**49-5**) by treatment with acetic anhydride. Reaction of this sugar-like derivative with uracyl (**49-6**) and trimethlysilyl triflate leads to the glycosidated nucleoside (**49-7**). Hydrogen peroxide then oxidizes the selenyl ether to a transient selenoxide; this then spontaneously splits out phenylselenous acid to leave behind a double bond (**49-8**). Removal of the silyl protecting group in that intermediate with fluoride ion then affords the HIV reverse transcriptase inhibitor **stavudine** (**49-9**) [50].
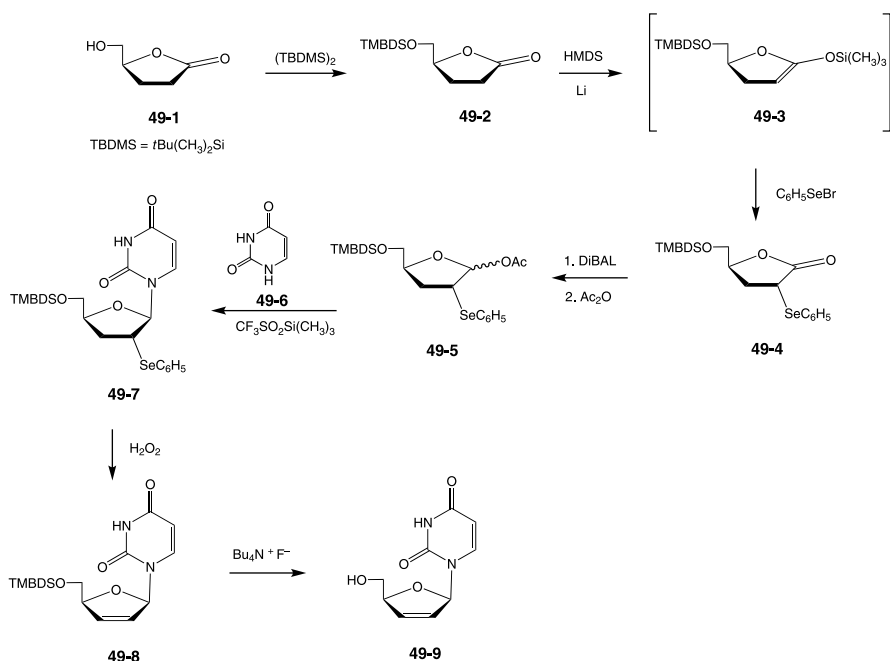
Relatively direct approaches lead to anti-HIV agents based on uridine and thymidine. Preparation of the first of these, **ralvudine** (**50-3**), starts by protecting 3′-deoxyuridine as it 5′-triphenylmethyl ether (**50-1**). The reagent DAST finds usage both as a strong dehydrating agent as above and for introducing fluorine. Thus, reaction of (**50-1**) with that reagent leads to the replacement of the hydroxyl at the 4′ position by fluorine with retention of the configuration (**50-2**). The protecting group at 5′ is then removed by treatment with acetic acid; the newly revealed hydroxyl is then converted to its acetate with acetic anhydride (**50-3**). Reaction with *N*-chlorosuccinimide then

chlorinates the pyrimidine ring to afford the 5-chloro derivative. Removal of the acetate at 5' by means of ammonia then affords **raluridine (50-4)** [51].
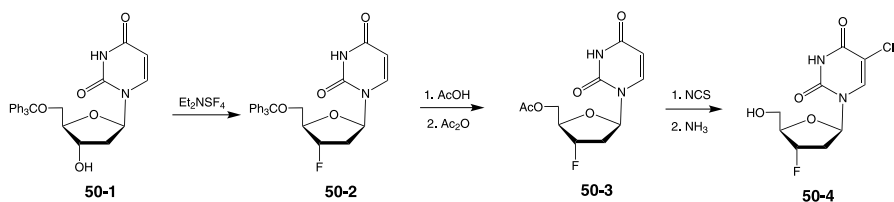
Synthesis of the thymidine derivative relies on the older two-step insertion of fluorine. Thus, the hydroxyl group in 3′-deoxythymidine benzoate (**51-1**) is first converted to the mesylate (**51-2**). Reaction with potassium fluoride in hydrogen fluoride replaces the mesylate by fluorine (**51-3**). The fact that this reaction, as that above, proceeds with retention of the configuration rules out simple displacement as the mechanism for this transform. The presence of the methyl group at position 5 negates the need for the chlorination step. Saponification then affords the antiviral agent **alovudine** (**51-4**) [52].
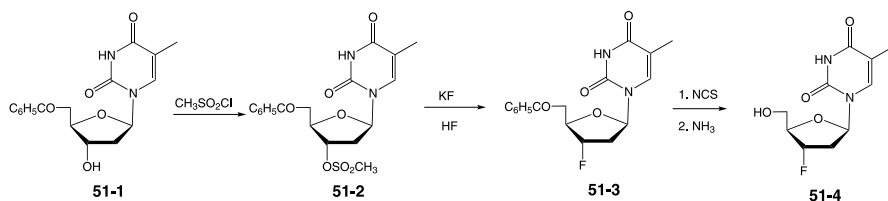
9.2.2.2.2. Compound with Surrogate Sugars. The rapid development of resistance to drugs, which is one of the hallmarks of HIV, has led to the continuing search for new antiviral agents. Replacement of one of the carbon atoms in the saccharide by another element has proven a particularly fruitful stratagem. Plentiful ascorbic acid (**52-2**) comprises the starting material for an early synthesis for **troxacitabine** (**52-10**). Reaction of (**52-2**) with the acetal from benzylglyoxal (**52-1**) forms the cyclic acetal (**52-3**) from the two terminal hydroxyls as a mixture of enantiomers. Oxidation with peroxide cleaves the furenone ring with a loss of a carbon atom to afford the hydroxyacid (**52-4**). Ruthenium trichloride next cleaves off the terminal carboxyl group to give (**52-5**). The two isomers are then separated by flash chromatography. Oxidation with lead tetraacetate disposes of the final carboxyl group with a concomitant transfer of an acetate (**52-6**). Catalytic hydrogenation results in the loss of the benzyl protecting group. The thus-revealed hydroxyl group is then acylated to afford the di-acetate (**52-7**). Glycosylation with cytidine is accomplished by the well-established method. Thus, the reaction of acetate (**52-7**) with the silylated derivative (**52-8**) in the presence of a Lewis acid leads to the coupling product (**52-9**) with a loss of the silyl groups. Separation of the

diastereomers followed by treatment with a dilute base affords the reverse transcriptase inhibitor **troxacitabine (52-10)** [53].
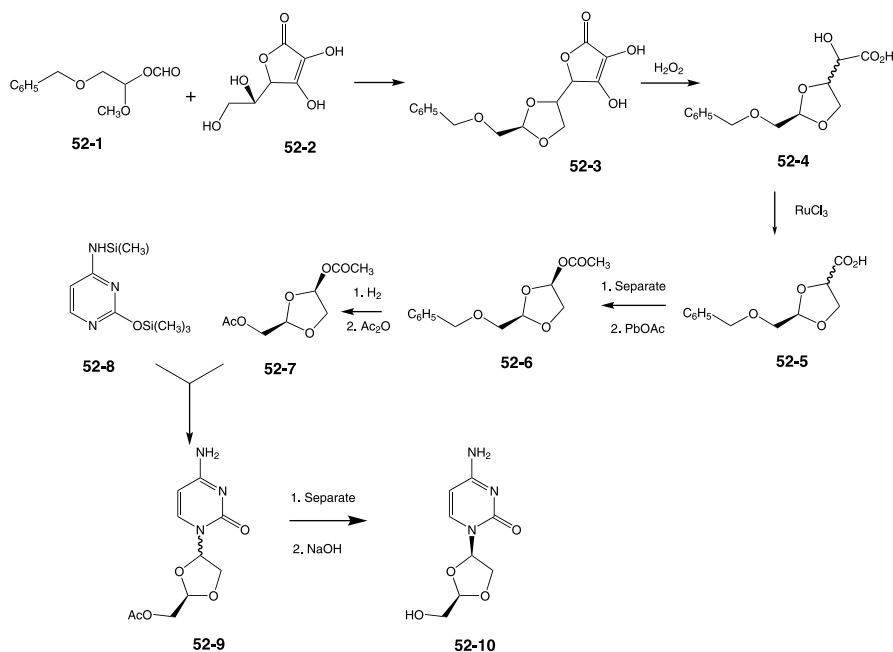
The isostere in which sulfur replaces the methylene group at the 4′ position in the furan ring of customary sugars also shows good activity as an inhibitor of HIV reverse transcriptase. The initial step consists of formation of the thioacetal (**53-3**) from glyoxal benzoate (**53-1**) and the methyl acetal of thioglyoxal (**53-2**). Reaction of
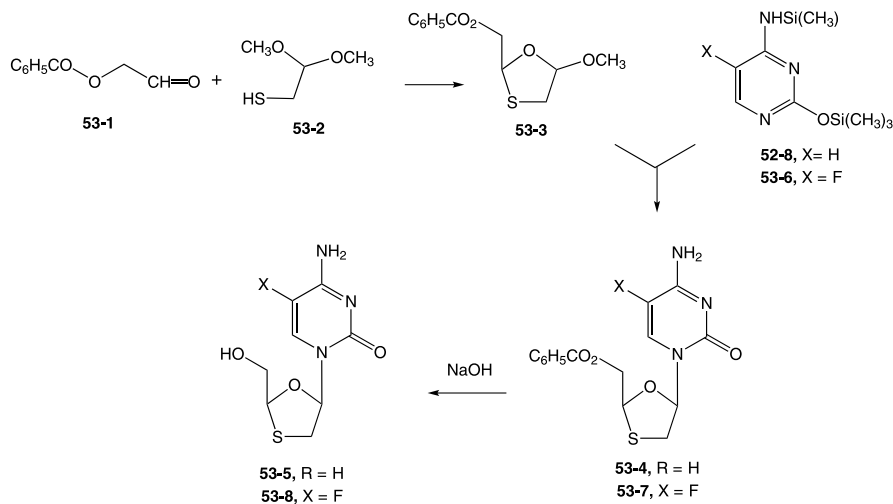
that with the silyl ether (**52-8**) leads to predominantly the desired anomer (**53-4**) of the glycosylated pyrimidine. The benzoate protecting group is then removed by treatment with an ion exchange resin to afford **lamivudine** (**53-5**) [54]. The same sequence using the silyl ether (**53-6**) from the fluorinated pyrimidine (**53-7**) leads to the reverse transcriptase inhibitor **emtricitabine** (**53-8**) [55].

The discovery of the antiviral agent acyclovir and later follow-on compounds, described in Chapter 15, revealed that good antiviral activity was observed in purines in which an open chain polyol replaces the saccharide. Detailed studies of those agents showed that the proximate active drug consisted of the phosphorylation products formed *in vivo*. The pyrimidine-based counterpart of those compounds incorporates a side chain bearing a phosphate group attached via a phosphorus-carbon bond resistant to *in vivo* cleavage. The synthesis of this compound starts by a reaction of *N*-benzoyluridine (**54-1**) with the chiral triphenylmethyl ether (**54-2**) of chiral glycidol to afford the alkylation product (**54-3**) as a single enantiomer. The alkoxide from the side chain hydroxyl is next allowed to react with the phosphite tosylate (**54-4**) to afford the phosphate ether (**54-5**). Treatment of that product with trimethylsilyl bromide cleaves the ethyl groups on the phosphite to yield the corresponding acid (**54-7**). Ammonolyis then removes the benzamide protetcting group to afford **cidofovir** (**54-8**) [56].
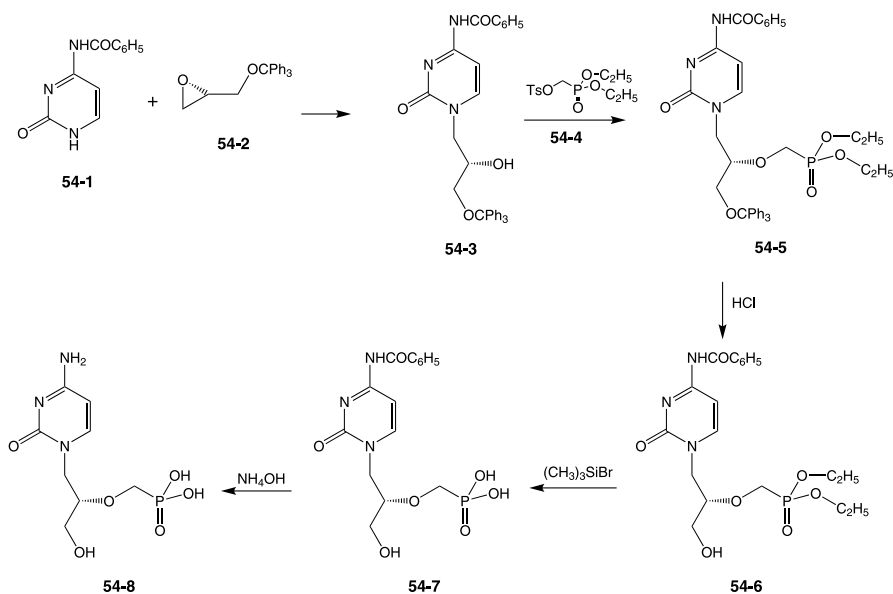
9.2.2.3. Miscellaneous Pyrimidines.

Excessive levels of thyroxin, as, for example, in Grave's syndrome, can lead to a host of serious problems. Those levels can be brought back to normal by the rather simple thiopyrimidine **propyl-thiouracil** (**55-4**), often better known by its acronym, **PTU**. The drug is available in a single step from reaction of the substituted acetoacetate (**55-1**) with thiourea (**55-2**) [57]. Though the order of the two required steps is not clear, the sequence can be visu-alized by assuming the intermediacy of the ester amide interchange intermediate (**55-4**).
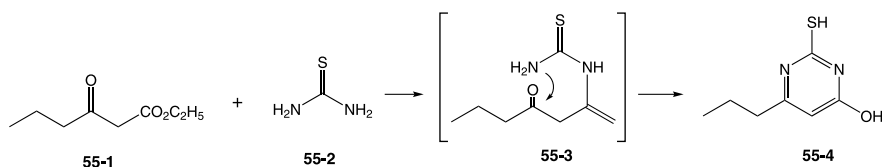
One of the most potent known hypotensive agents incorporates an *N*-oxide function in addition to the amidine moiety usually associated with vasodilators. It was adventitiously noted in the course of clinical trials for the treatment of refractory hypertension that use of the compound stimulated unusual new hair growth. This was confirmed by clinical observations after the drug was approved as an antihypertensive. Further studies showed that the hair growth stimulation could be obtained in appropriate cases when the drug was administered topically, an important consideration for an agent that exerts such profound effects on systemic administration. This compound, **minoxidil** (**56-5**), has been available for some years as Rogaine® (the FDA rejected Regain as a trade name) as a nonprescription drug for the treatment of male pattern baldness. An expeditious synthesis starts with the cyanomalonamide (**56-1**); this is then converted to its methyl enol ether (**56-2**), for example, by reaction with trimethyloxonium fluoroborate. Reaction of that intermediate with cyanamide leads to the imine (**56-3**). Condensation with hydroxylamine can occur at either cyano group; for clarity, only one alternative is shown. Addition to that on nitrogen
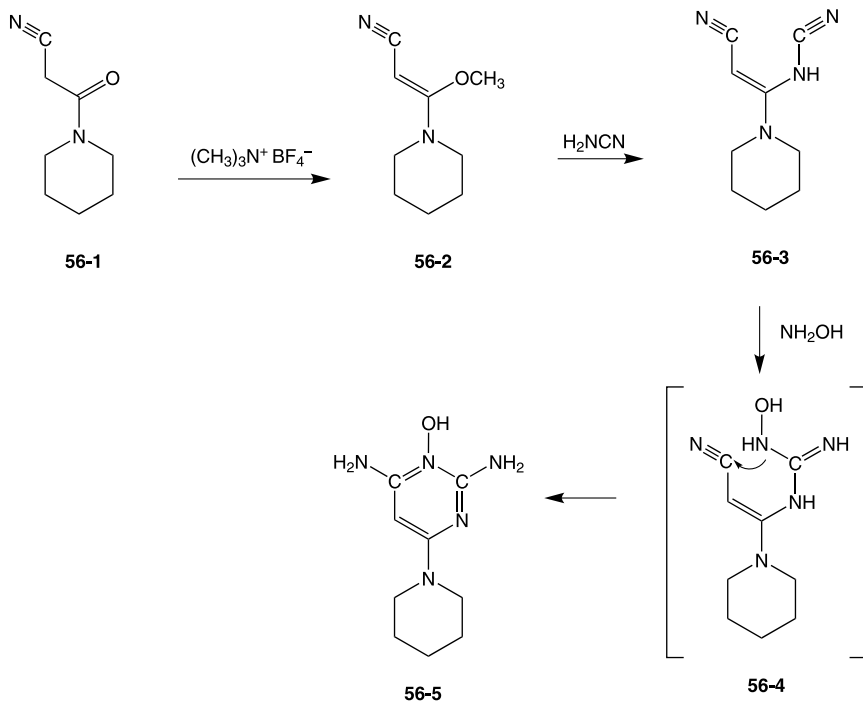
will lead to the formation of the hypothetical hydroxyguanidine (**56-4**). Addition to the remaining nitrile leads to **minoxidil** (**56-5**) after bond rearrangement [58].

The search for endothelin antagonist as potential compounds for treating cardiovascular disease was noted in the preceding chapter (see **atrasentan**). A structurally considerably simpler example incorporates a pyrimidine ring in the side chain. Condensation of benzophenone (**57-1**) with ethyl chloroacetate and sodium methoxide proceeds initially to the addition of the enolate from the acetate to the benzophenone carbonyl. The alkoxide anion on the first-formed quaternary carbon then displaces chlorine on the acetate to leave behind the oxirane in the observed product (**57-2**). Methanolysis of the epoxide in the product in the presence of boron trifluoride leads to the ether alcohol (**57-3**). Reaction of this with the substituted pyrimidine (**57-4**) in the presence of a base leads to the displacement of the methanesulfonyl group on the heterocycle by the alkoxide from (**57-3**). Saponification of the ester group in that product gives the corresponding acid, **ambrisentan** (**57-5**) [59].
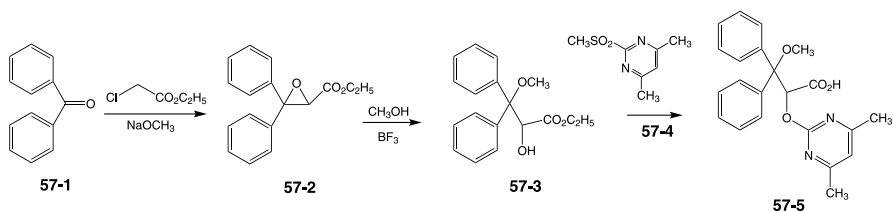
An entire new field of therapeutics arose with the serendipitous discovery of the effect on erectile function of **sildefanil** (see Chapter 15), far better known as Viagra®. The enormous and still rising market opened by that drug has predictably led to the search for other inhibitors of phosphodiesterase 5, the enzyme responsible for this activity. The structures of many follow-on agents have hewed fairly close to the original PDE 5 inhibitor. Others, such as **avanafil** (**58-9**), differ markedly from sildefanil in structure. The synthesis of this agent in effect consists of a series of displacement reactions. Thus, reaction of the benzylamine (**58-1**) with chloropyrimidine
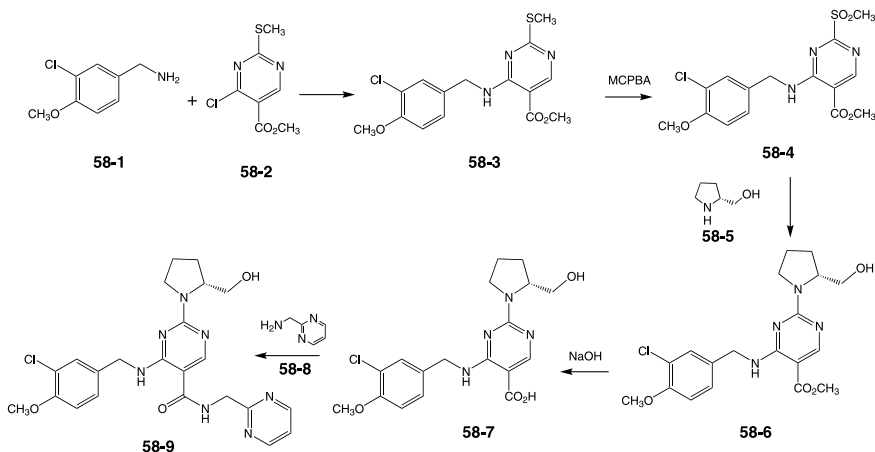
(**58-2**) leads to the displacement of chlorine and the formation of the coupling product (**58-3**). The inert methylthio ether on the pyrimidine ring is made labile by conversion to a sulfoxide (**58-4**) by means of *meta*chloroperbenzoic acid. Reaction of that product with L-prolinol (**58-5**) leads to the replacement of the sulfoxide by the basic nitrogen in (**58-5**) and the formation of the coupling product (**58-6**). The ester group in this last intermediate is then hydrolyzed to afford the corresponding acid (**58-7**). Reaction of this acid with 1-aminomethylpyrimidine (**58-8**) in the presence of a carbodiimide leads to the amide (**58-9**) and thus **avanafil** [60].

9.2.3. Pyrimidones

The great majority of antiulcer compounds fall neatly into the category of histamine H_2 antagonists or inhibitors of the sodium-potassium pump that drives gastric acid secretion. A relatively simple pyrimidone, on the other hand, does not fit either category. The compound inhibits acid secretion in animal models and also interestingly acts as a bronchodilator in histamine-challenged animals. The synthesis of this agent starts with the alkylation of *meta*-cresol (**59-1**) with the dimethyl acetal from chloro-acetaldehyde. Reaction of the product (**59-2**) with dimethylformamide acetal affords the formylation product (**59-3**) on workup. Treatment of that intermediate with urea can be visualized as proceeding to (**59-4**) by displacement of the dimethylamino group by urea nitrogen. Ring closure with the aldehyde carbonyl results in the formation of the pyrimidone ring; there is thus obtained **tolimidone** (**59-5**) [61].
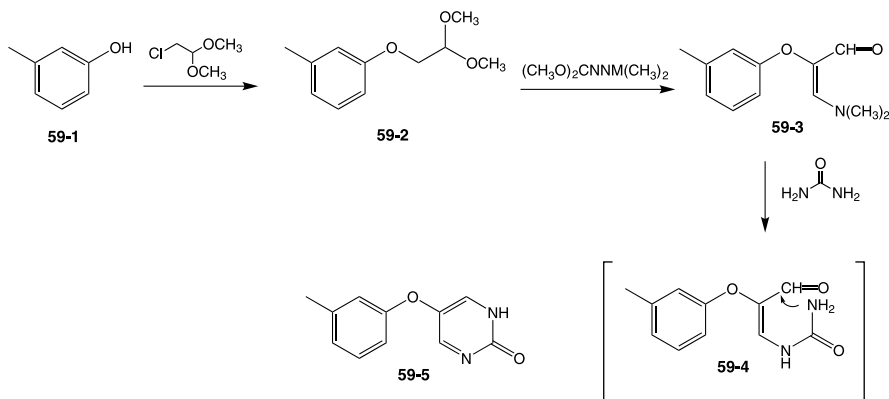
The key to changing the activity of histamine-related compounds from agonists to antagonist, as noted in the preceding chapter (see **cimetidine**), involved modifying the side chain amine to a thiourea-like function. The large amount of work devoted to H_2 blockers revealed that guanidine function embedded within a 2-amino-pyrimidone would serve as a surrogate thiourea, as exemplified by **oxmetidine**, also described in Chapter 8. Base-catalyzed condensation of picoline-5-aldehyde (**60-1**) with the half-ester of ethyl malonate gives the corresponding acrylic ester; the initial adduct decarboxylates in the course of the reaction. Catalytic hydrogenation then affords the propionic ester (**60-2**). Treatment with ethyl formate in the presence

of sodium ethoxide affords the formylated product (**60-3**). The reaction of the result-ing 1,3 dicarbonyl compound with nitroguanidine (**60-4**) proceeds in a manner analogous to that described above for urea, to give the pyrimidone (**60-5**). The nitro group transforms the amino group at the 2 position of the pyrimidine into a leaving group. Displacement of that group by the primary amine in pyridylbutyl-amine (**60-6**) affords the alkylation product and thus **icotidine** (**60-7**) [62].
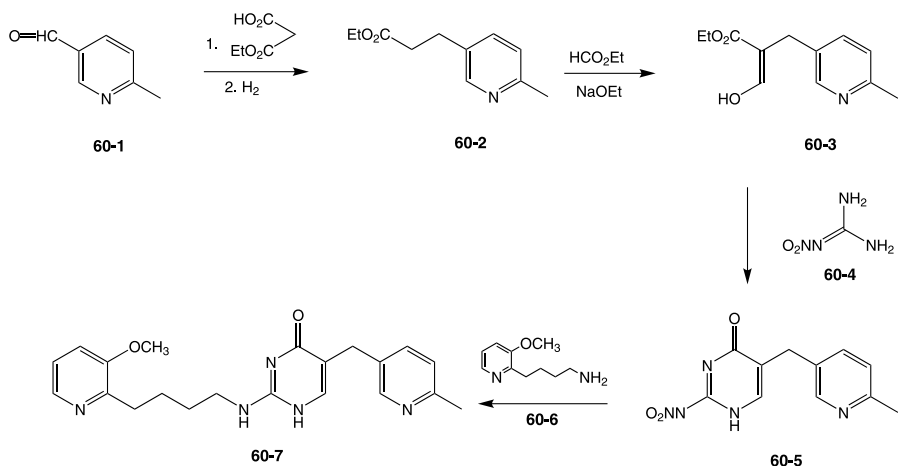
In a similar vein, the displacement of the nitrated amino group in pyrimidone (**61-2**), prepared in the same way as (**60-5**) using the methoxyl pyridinealdehyde, with the **ranitidine** nucleus (**61-1**) affords the H$_2$ blocker **donetidine** (**61-4**) [63] after cleavage of the methyl ether.
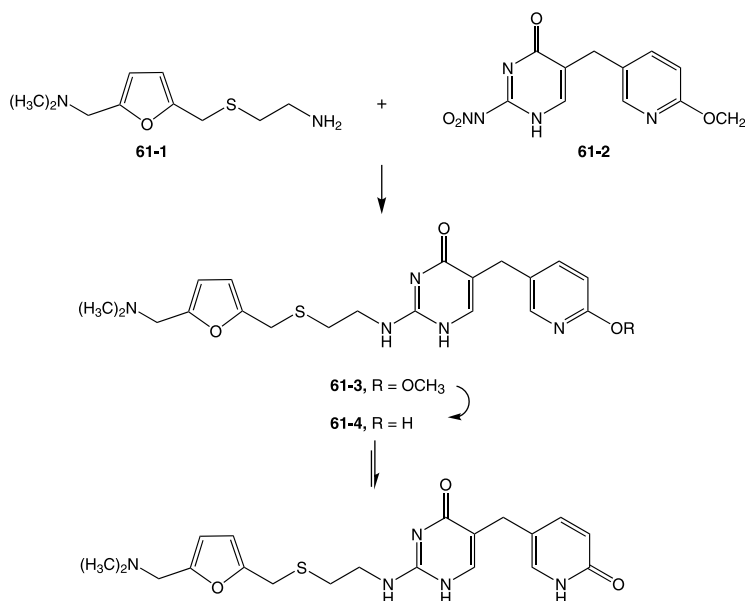
An alternate approach to the preparation of the side chain involves reaction of picoline-5-aldehyde (**60-1**) with the pyrimidone (**62-1**). Benzal-like condensation of the aldehyde with the enamide function in (**62-1**) results in the formation of the bicyclic product (**62-2**), shown as the keto tautomer. The double bond is then removed by catalytic hydrogenation (**62-3**). Treatment of that intermediate with phosphorus oxychloride leads to the replacement of the imide carbonyl group by chlorine via its enol tautomer. Displacement of halogen by means of sodium methoxide gives the corresponding methyl ether (**62-4**). Displacement of that ether by the terminal amino group in the **ranitidine** nucleus (**61-1**) gives the antiulcer agent **lupitidine** (**62-5**) [64].
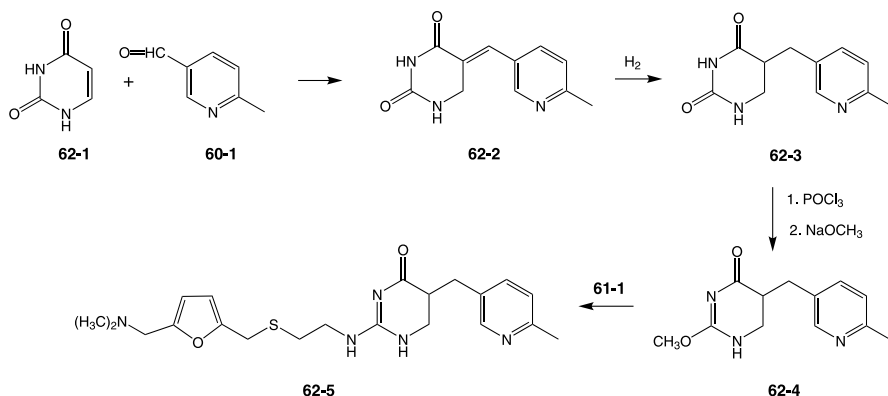
Cardiotonic activity is retained when the pyridone ring in the cardiotonic agent **milrinone** (**26-3**) is replaced by a pyrimidone. The reactive starting material (**63-1**) is available by base-catalyzed condensation of ethyl cyanoacetate with carbon disulfide followed by treatment of the intermediate with methyl iodide. Reaction of the product with acetamidine (**63-2**) can be visualized as involving the replacement of one of the thiomethyl groups by amidine nitrogen. The initial step would thus yield the addition-elimination product (**63-3**). Attack on the ester carbonyl by the second amidine nitrogen will lead to the pyrimidone intermediate (**63-4**). Reaction of that product with 2-aminomethylpyridine (**63-5**) then leads to the replacement of the thiomethyl group by the more basic amine. This affords the cardiotonic agent **pelrinone** (**63-6**) [65].
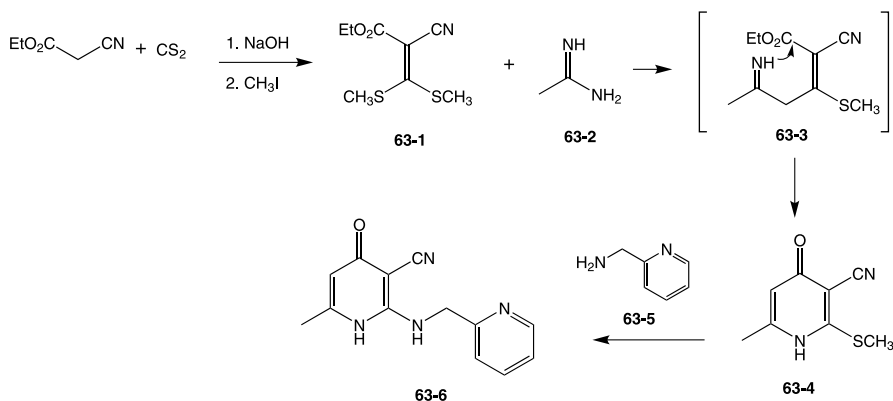
A relatively simple pyrimidone, **bropirimine** (**64-3**), has been extensively studied as an antitumor agent and immune modulator as a consequence of its unusual activity as an interferon inducer. Condensation of ethyl benzoylacetate (**64-1**) with guanidine leads to the pyrimidone (**64-2**) by a sequence quite analogous to those outlined above. Treatment of that product with bromine leads to bromination at the sole open position on the heterocyclic ring to afford **bropirimine** (**64-3**) [66].
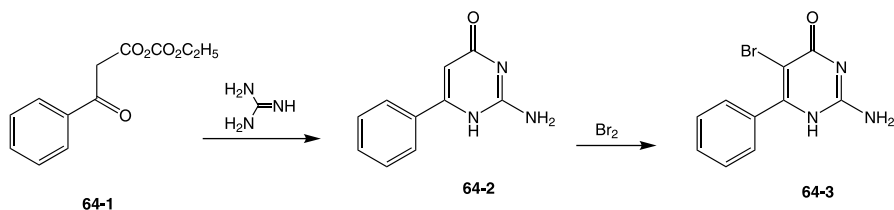
Development of drug-resistant strains is a recurring theme in the discussion of antiviral drugs for treating HIV. This problem seems to arise as each class of drugs comes into use and is by now well established for both reverse transcriptase and protease inhibitors. There is thus considerable interest in finding drugs that interrupt the natural history of the virus at yet different stages. Maraviroc (Chapter 8) and aplaviroc, described below, comprise very recently developed representatives of a series of agents that block cell surface receptors that allow the virion to enter the cells. These various mechanisms are now complemented by an agent that inhibits the integrase enzyme that inserts viral DNA into the infected cell's genome. The
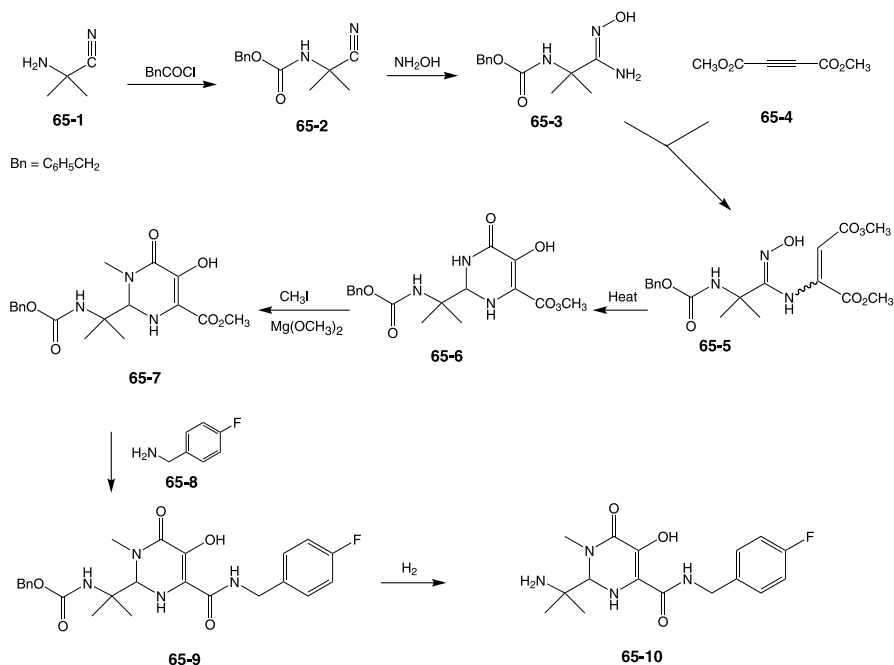
convergent synthesis of this compound, **raltegravir** (**66-5**), involves an unusual method for building a pyrimidone ring. The sequence starts by protecting the amine on the α-aminonitrile (**65-1**) from acetone as its carbobenzyloxy derivative (**65-2**) by reaction with carbobenzyloxy chloride. Reaction with hydroxylamine leads to the amidoxime (**65-3**). Treatment of that product with dimethyl acetylenedicarboxylate (**65-4**) leads initially to the conjugate addition of basic nitrogen to give the condensation product (**65-5**) as a mixture of geometric isomers. That product then cyclizes to the pyrimidone (**65-6**) on heating. Treatment of the pyrimidone with methyl iodide in the presence of magnesium methoxide leads to the alkylation of the more accessible pyrimidone nitrogen and the formation of (**65-7**). An ester-amine interchange with 4-fluorobenzylamine (**65-8**) then leads to the amide (**65-9**). Catalytic hydrogenation over palladium then removes the carbobenzyloxy protecting group (**65-10**).

In the convergent scheme, the salt from the treatment of tetrazole (**66-1**) with a base is acylated with the half-ester of oxalyl chloride to afford the acylation product (**66-2**). This undergoes rearrangement to the oxadiazole (**66-3**) on heating. The reaction may be rationalized by invoking an attack by oxygen on the amide-like carbonyl on the carbon bearing the methyl group to form the new heterocycle with a concomitant extrusion of neutral nitrogen. The ester is next saponified and the resulting acid (**66-3**) converted to the corresponding acid chloride (**66-4**). Reaction of this last intermediate with the amine of the product from the other arm of the synthesis (**65-10**) then affords the antiviral agent **raltegravir** (**66-5**) [67].
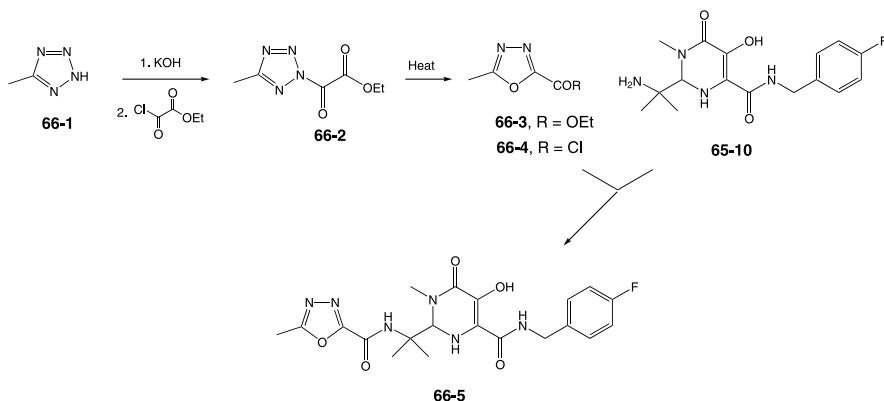
9.2.4. Triketopyrimidines: The Barbiturates

The barbiturate sedative-hypnotic agents arguably constitute the oldest class of medicinal agents whose synthesis was not prompted by some biologically active natural product. The first compound in this series, **barbital** (**67-3**) ($R^1 = R^2 = Et$), has been in continuous use since at least 1903. The persisting consumption of these compounds is somewhat puzzling in view of their now well-recognized shortcomings. These drugs, for example, exhibit significant abuse potential that readily crosses

over with alcohol abuse. The quality of sleep induced by these drugs is held to be poor and resistance to the hypnotic potential seems to develop relatively quickly in most individuals. All active barbiturates fit the general formula (**67-3**), with obligatory substitutents at both *R* groups. The general method for the preparation of these compounds involves base-catalyzed condensation of a malonic ester (**67-2**), or its cyanoacetate equivalent, with urea. An alternative consists of reaction with guanidine to form the imino derivative (**67-5**) followed by acid hydrolysis. The same reaction with thiourea gives thiobarbiturates such as (**67-4**). These last are quickly metabolized to inactive species, making their use ideal when a short duration of action is indicated.
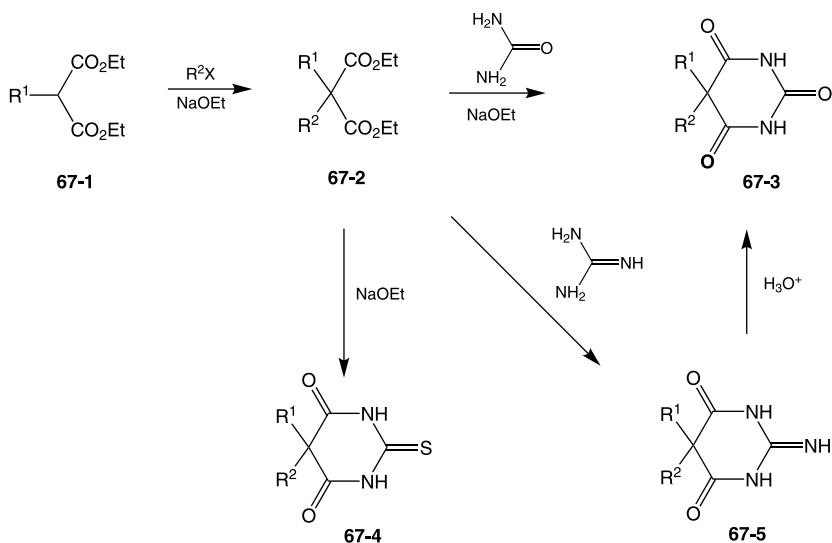
The straightforward step used to form the ring system means that the chemistry involved in the preparation of the scores of barbiturates that have been used clinically in fact devolves on the syntheses of the various malonic esters. It should be noted that little success has been achieved in changing the side effect spectrum of these drugs. The main differences between the various agents involve their pharmacokinetic properties; these in turn are manifested as variations in bioavailablity by parenteral and oral routes as well as in time to the onset and duration of action.

9.2.5. Pyrazines

Only a very few therapeutic agents, in marked contrast to the large number of entities that contain a pyrimidine ring, are based on the pyrazine ring, One of those, the antitubercular antibiotic **pyrazinamide** (**68-6**), probably acts by a similar mechanism as its pyridine parent, **isoniazide**. The tonnage chemical *ortho*-phenylene diamine (**68-2**) provides a convenient route to pyrazines. Thus condensation of that diamine with glyoxal (**68-1**) leads to quinoxaline (**68-3**). Treatment of the heterocycle with

a strong oxidant such as permanganate leads to selective cleavage of the benzene ring and the formation of the dicarboxylic acid (**68-4**). Heating of this intermediate leads to a loss of one of the carboxyl groups. The resulting carboxylic acid is then converted to its ethyl ethyl ester (**68-5**) with ethanolic hydrogen chloride; an amide-ester interchange with ammonia then affords **pyrazinamide** (**68-6**) [68].
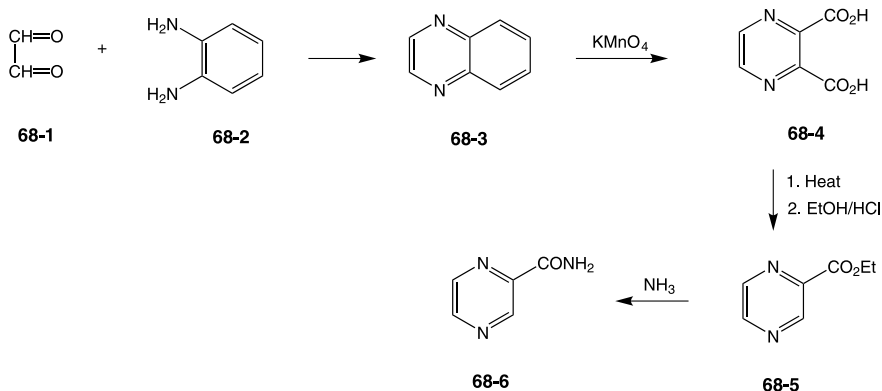
One shortcoming of the thiazide diuretics is their tendency to cause excessive loss of potassium. The so-called potassium sparing diuretics, the most important of which is based on a pyrazine ring, are often used when loss of potassium is a potential problem. The dicarboxylic acid (**68-4**), described above, provides the starting material for this drug as well. The acid is first esterified with ethanol. Treatment of that ester with ammonia affords the corresponding *bis* amide (**69-1**). Exposure of that amide to a single equivalent of sodium hypobromite leads to selective Hoffmann rearrangement of but one of the two amide groups and the formation of the amino-amide (**69-2**). Alcoholysis of that intermediate leads to the conversion of the carboxyl group to its ester; reaction with sulfuryl chloride results in the chlorination of the two open ring positions to the dichloro compound (**69-3**). Reaction of that product with ammonia leads to the displacement of the halogen *para* to the carboxyl group
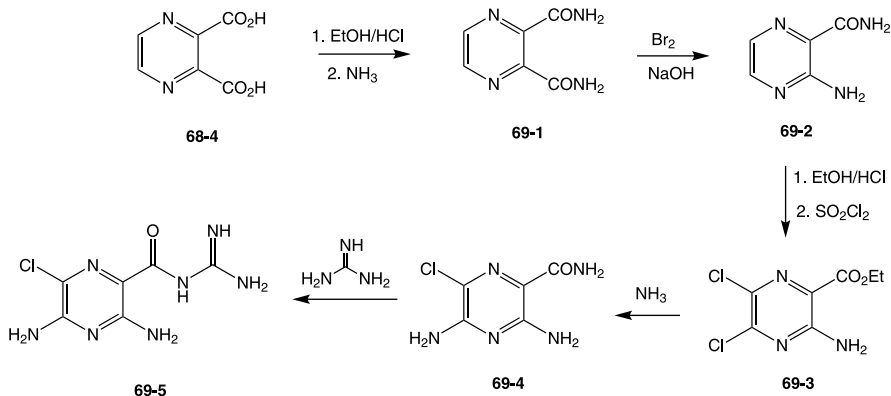
and the formation of the corresponding diamine; ammonia concurrently converts the ester back to the amide to afford (**69-4**). Treatment of this last intermediate with guanidine leads to the formation of an acyl-guanidine function by an exchange reaction. There is thus formed **amiloride** (**69-5**) [69].

Amides that bear an amino group at the 2 position provide a more direct route to less highly substituted pyrazines. Thus, reaction of 2-aminomalonamide (**70-1**) with glyoxal leads in a single step to the pyrazine (**70-2**). The superfluous carboxyl is removed in this case by first hydrolyzing the amide to its corresponding acid (**70-3**) and then thermolyzing that intermediate to give (**70-4**). The hydroxyl group is then replaced by chlorine by means of phosphorus oxychloride (**70-5**). The displacement of chlorine with dimethylamine gives **ampyzine** (**70-6**) [70]. This compound is described as a central CNS stimulant.
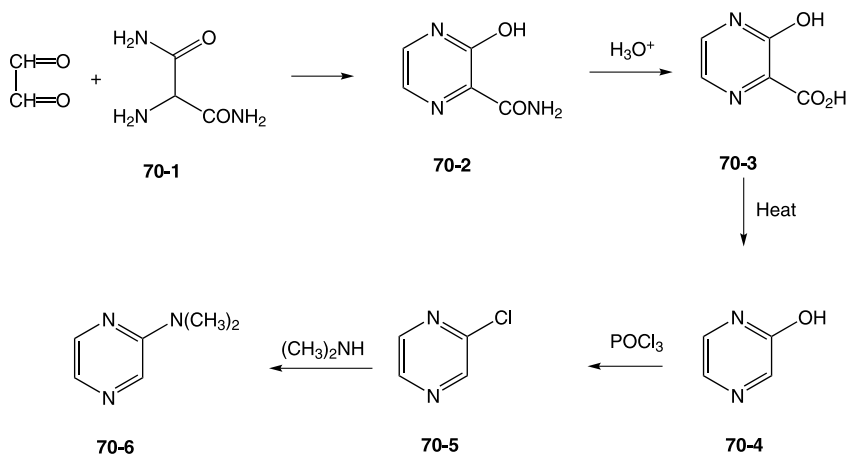
The synthesis of the trimethyl analogue of (**70-6**) represents the most direct approach to the pyrazine system. In this case, condensation of *R,S*-alaninamide (**71-1**) with diacetyl gives the pyrazinol (**71-2**) directly. The hydroxyl group is then converted to the corresponding dimethylamine by the same sequence as above [71]. The product, **triampyzine** (**71-3**), shows predominantly anticholinergic activity.
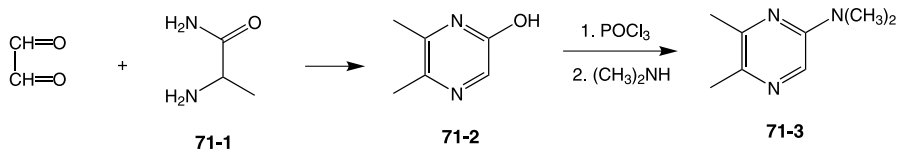
9.2.6. Piperazines

Piperazines, in contrast to pyrazines, abound in medicinal agents; that moiety quite often occurs in side chains serving as a surrogate tertiary amine or as an ethylenediamine. A number of these have already been covered in passing in earlier chapters. The examples that follow have been chosen to illustrate the varied synthetic strategies

that have been used to incorporate those structural fragments. In addition, the "spirone" anxyolytic agents are included in some detail since the common occurrence of the piperazines in this class suggests that the moiety may in this case form part of a pharmacophore.

Selective reaction of but one of the nitrogen atoms on piperazine can be assured by the use of protecting groups. Thus, alkylation of the benzyl derivative (**72-1**) with ethyl chloroacetate gives the alkylation product (**72-2**). The protecting group is then removed by hydrogenation over palladium (**72-3**). Acylation of the newly revealed secondary amine with 3,4,5-cinnamoyl chloride (**72-4**) affords the **cinepazet** (**72-5**) [72], a compound that shows antianginal activity.
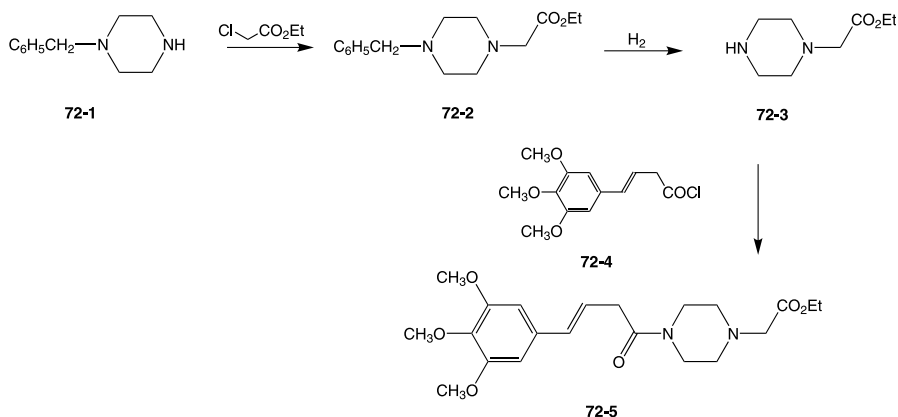
A somewhat more complex antianginal compound incorporates the xylylamide function that is often found in local anesthetic-based antiarrhythmic agents as well as a moiety reminiscent of β-blockers. The synthesis in fact starts with a ring opening of the oxirane in the familiar β-blocker intermediate (**73-1**) with piperazine to give the mono alkylation product (**73-2**). (The fact that the resulting propanolamine side chain amine is tertiary rather than secondary makes it questionable whether the compound has adrenergic activity.) In a convergent sequence, acylation of 2,6-xylidine
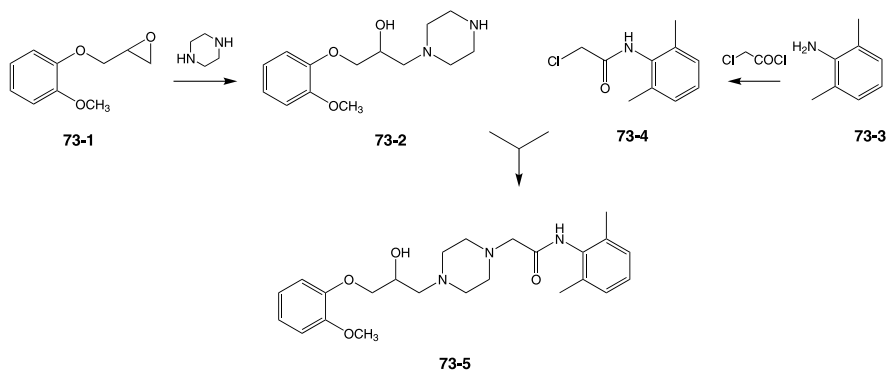
(**73-3**) with chlororacetyl chloride leads to the chloroamide (**73-4**). Alkylation of the free amine on the piperazine (**73-2**) with (**73-4**) gives **ranolazine** (**73-5**) [73].

The structures for the original venerable antihistamines often included an ethylene-diamine side chain on the assumption that this would better mimic histamine itself. This side chain was modified to a piperazine in some of the more effective agents. Alkylation of the free amine in the mono carbamate (**74-2**) from piperazine with the benzhydryl chloride (**74-1**) gives the tertiary amine (**74-3**); the protecting group is then removed by sequential saponification in a base to the carbamic acid, followed by treatment with a mild acid. Alkylation of the intermediate (**74-4**) with 2-chlor-oethoxyethanol affords the potent H_1 antihistamine **hydroxyzine** (**75-4**) [74]. One of the principal metabolites of this drug consists of the carboxylic acid from the oxidation of the terminal alcohol. This product was found to be an orally effective antihistamine in its own right. The compound is further nonsedating since the polar acid group prevents its penetration into the CNS. This agent can be prepared by alkylation of intermediate (**74-4**) with 2-chloroethoxyacetamide (**74-6**) followed by hydrolysis of the amide group. This gives the nonsedating antihistamine **cetirizine** (**74-7**) [75].
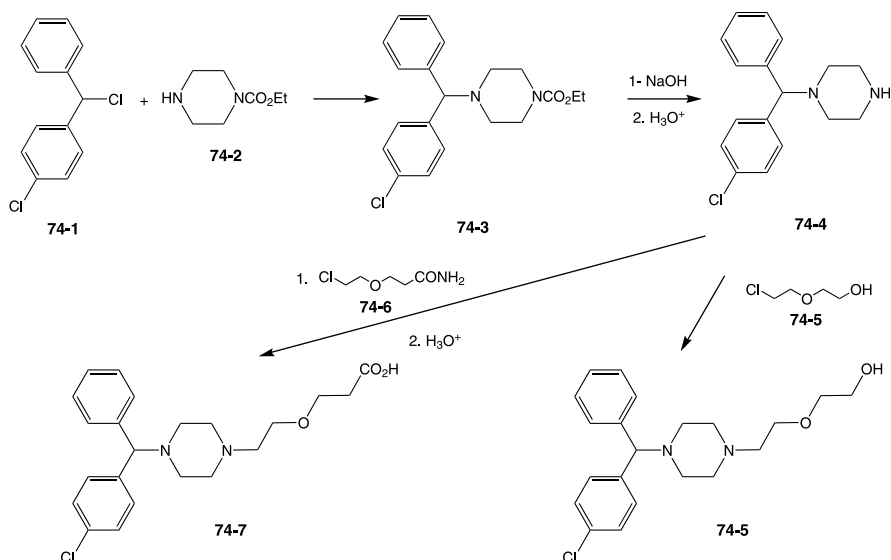
A perusal of the structures of compounds that display CNS activity will reveal that a sizeable number of those agents incorporate a piperazine moiety. The chemistry of the agents involves largely successive alkylation reactions, once the piperazine ring is in place. That ring in the antipsychotic agent **fluanisone** (**75-4**) apparently serves the same role as does the piperidine in the prototype butyrophenone **haloperidol** (**18-8**). Reaction of *ortho*-anisidine (**75-1**) with diethanolamine (**75-2**) and hydrogen chloride in all probability proceeds by alkylation of the aniline by the nitrogen mustard that is formed *in situ*. Alkylation of the product (**75-3**) with the **haloperidol** intermediate (**20-1**) affords **fluanisone** (**75-4**) [76].
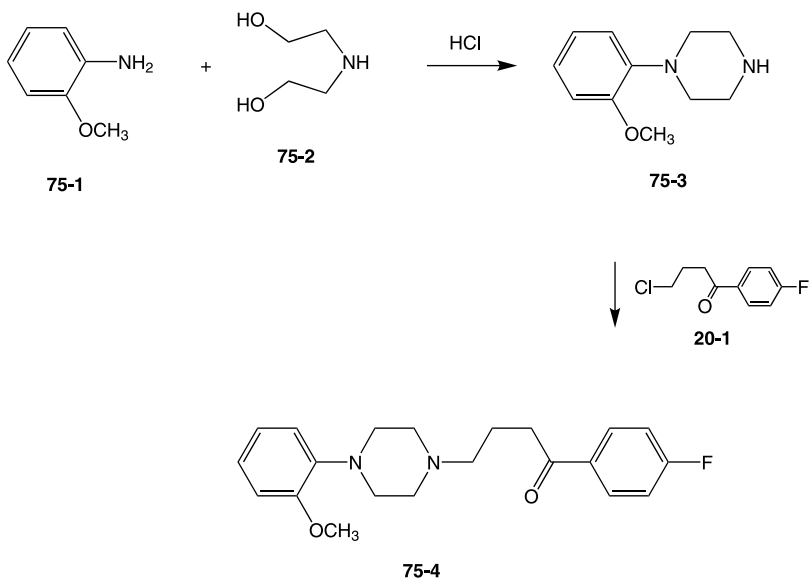
The synthesis of the antipsychotic agent **mazapertine** illustrates a use of the nitro-gen mustard *bis*-(2-chloroethyl)amine for building a piperazine ring. Alkylation of *ortho*-nitrophenol (**76-1**) with isopropyl bromide leads to the corresponding isopropyl ether (**76-2**). Catalytic hydrogenation then reduces the nitro group to the aniline (**76-3**). Reaction of this last intermediate with nitrogen mustard (**76-4**) yields the *bis*-alkylation
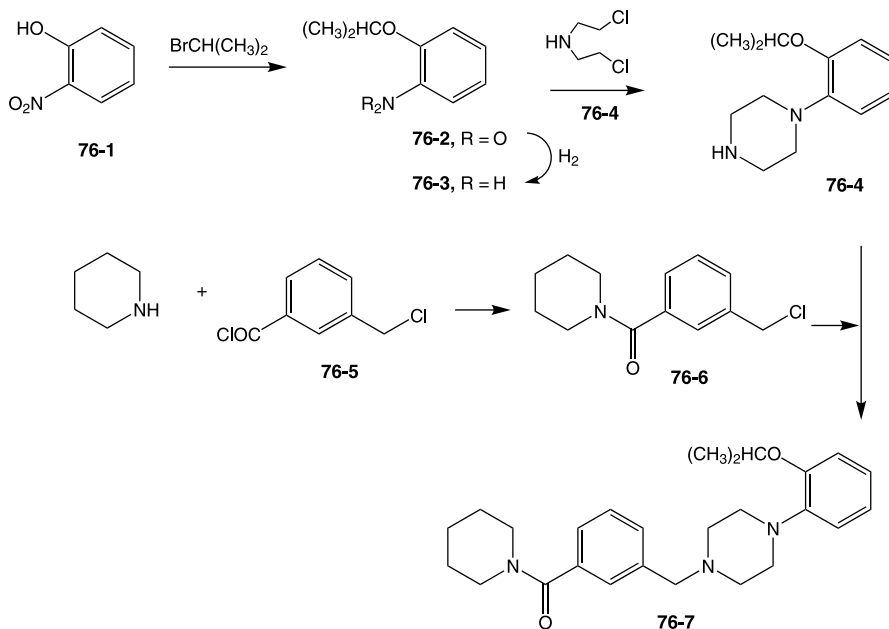
product, piperazine (**76-4**). In a convergent sequence, acylation of benzoyl chloride (**76-5**) with piperidine leads to the amide (**76-6**). Reaction of this last intermediate with piperazine (**76-4**) leads to the displacement of the benzylic halogen in (**76-6**) by piperazine nitrogen to afford the alkylation product mazapertine (**76-7**) [77].

In an analogous manner, reaction of 2,3-dichloroaniline (**77-1**) with nitrogen mustard gives the arylpiperazine (**77-2**). The remaining amine is then alkylated with 4-chlorobromobutane (**77-3**). Alkylation of the alkoxide from the hydroxycarbostyril (**77-4**) affords the antipsychotic agent **aripiprazole** (**77-5**) [78].
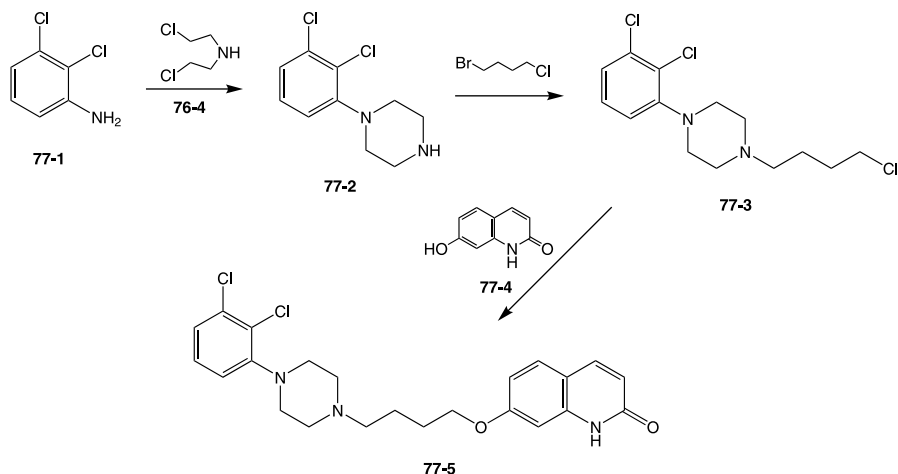
The large majority of antipsychotic drugs act mainly as dopamine receptor antagonists reducing the excess responsiveness to that neurotransmitter present in psychoses. It was found a decade ago that antagonists of serotonin H$_2$ showed promising antipsychotic activity in several model systems. These drugs would be better tolerated than their predecessor since they should be devoid of side effects
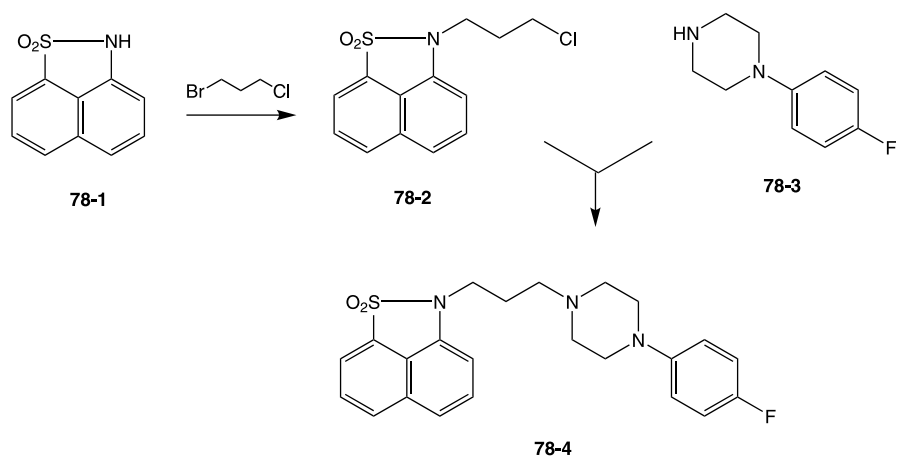
traceable to the blockade of dopamine receptors. The synthesis of one of these also comprises sequential alkylation reactions. Thus, alkylation of the anion from naphthosultam (**78-1**) with 4-chlorobromobutane affords (**78-2**). Reaction of that intermediate with *N*-(4-fluorophenyl)piperazine (**78-3**) leads to the serotonin H$_2$ antagonist **fananserin** (**78-4**) [79].

The classical tricyclic antidepressant drugs, which are discussed in Chapter 13, manifest a set of structure-specific side effects that are thought to be due to their shared anticholinergic activity. Two of the first antidepressant agents that depart from the tricyclic motif, and do not manifest the side effects typical of the older drugs, are built around aryl piperazine moieties. It should be noted that a three-carbon chain connects the piperazine fragment with the heterocyclic moiety in both these compounds The seemingly complex bicyclic heterocyclic nucleus included in **trazodone** (**79-6**) is, in fact, constructed in a single step by reaction of 2-chloropyridine (**79-1**) with semicarbazone. The first step can be envisaged as the formation of the displacement product (**79-2**). Attack of the pyridine nitrogen on the carbonyl group with an expulsion of ammonia will then afford (**79-3**) after bond reorganization. The second half of the molecule is obtained by alkylation of *N*-(3-chlorophenyl)piperazine (**79-4**) with 3-bromo-1-chloropropane to afford (**79-5**). Reaction of the anion from (**79-3**) with chloroalkylamine (**79-5**) leads to the alkylation product; there is thus obtained **trazodone** (**79-6**) [80].
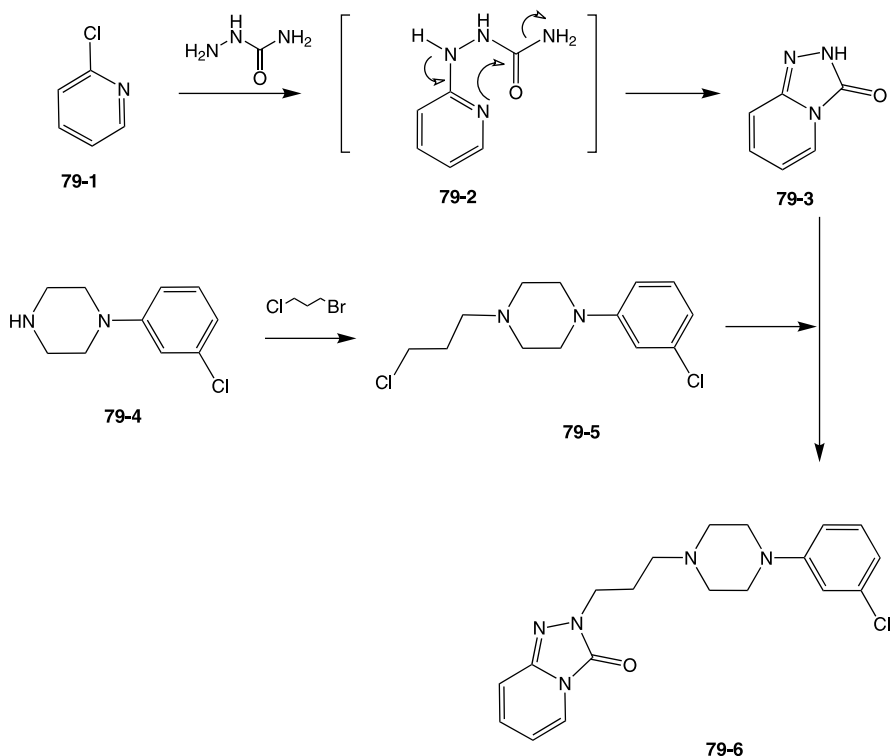
Preparation of the closely related antidepressant **etoperidone** (**80-6**) illustrates a different approach to the piperazine ring. The first step in this synthesis involves the alkylation of the anion from triazinone (**80-1**) with 3-bromo-1-chloropropane to afford (**80-2**). The displacement of chlorine in that intermediate by the amino group in diethanolamine affords the corresponding *bis*-hydroxyethyl derivative (**80-3**); the hydroxyl groups are then converted to chlorine by treatment with thionyl chloride to give the substituted nitrogen mustard (**80-4**). Reaction of that product with *meta*-chloroaniline (**80-5**) leads to a piperazine ring formation; there is thus obtained **etoperidone** (**80-6**) [81].
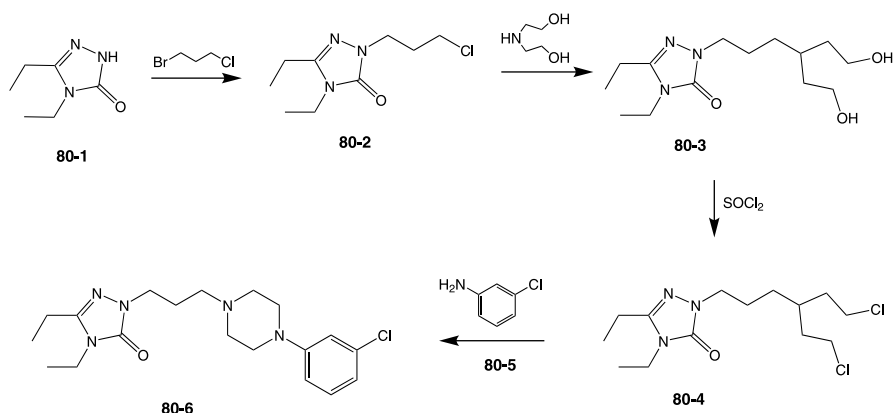
Piperazines also form an integral part of a series of anxiolytic drugs whose structures differ significantly from other tranquilizers. These agents act via a quite different mechanism than do the better-known benzodiazepines, which are discussed in Chapter 12; they do not, for example, bind to benzodiazepine receptors and do not show the typical side effects of the older tranquilizers. The preparation of the prototype, **buspirone** (**81-7**), starts with the displacement of chlorine in 2-chloropyrimidine (**81-1**) by piperazine to afford the mono-alkylation product (**81-2**). Alkylation of the remaining free amino group with 4-chlorobutyronitrile (**81-3**) gives the nitrile (**81-4**); the nitrile group is then reduced to the primary amine (**81-5**) by means of lithium aluminum hydride. The spirocyclic glutaric anhydride (**81-6**) used in the next step can be obtained by an unusual aldol-like condensation of ethyl acetate with
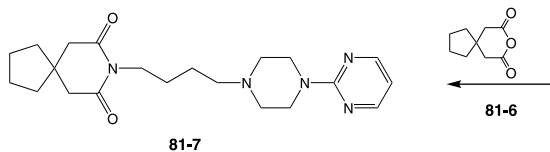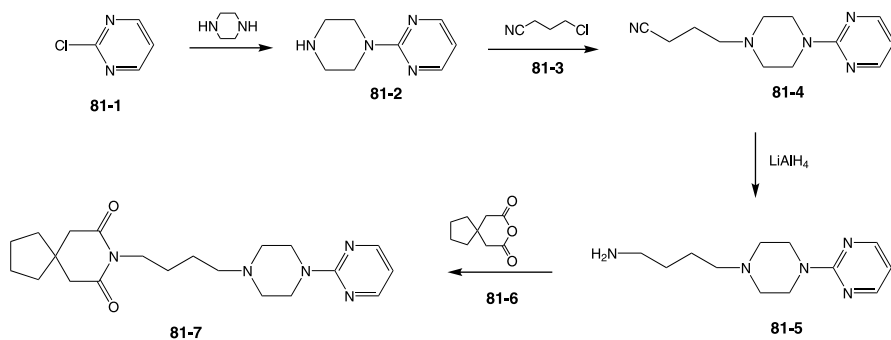
cyclopentanone, with the second acetate fragment being incorporated by conjugate addition to the dehydration product of the initial aldol product; saponification followed by treatment with acetic anhydride completes the scheme. Reaction of the primary amine (**81-5**) with the anhydride (**81-6**) leads to the formation of the corresponding glutarimide and thus **buspirone** (**81-7**) [82].

The strategy for the preparation of a nonspirocyclic analogue involves a string of alkylation reactions. Thus, treatment of 3,3-dimethyl glutarimide (**82-1**) with 4-bromo-1-chlorobutane gives the chlorobutyl intermediate (**82-2**). Use of that product to alkylate ethylene diamine then gives the intermediate (**82-3**). Reaction with 2-chloropyrimidine (**81-1**) leads to the replacement of chlorine by the terminal primary amino group to give (**82-4**). The central piperazine ring is then built by sequential alkylation of the two secondary amino groups in (**82-5**) with ethylene dichloride. There is thus obtained the anxiolytic agent **gepirone** (**82-5**) [83].
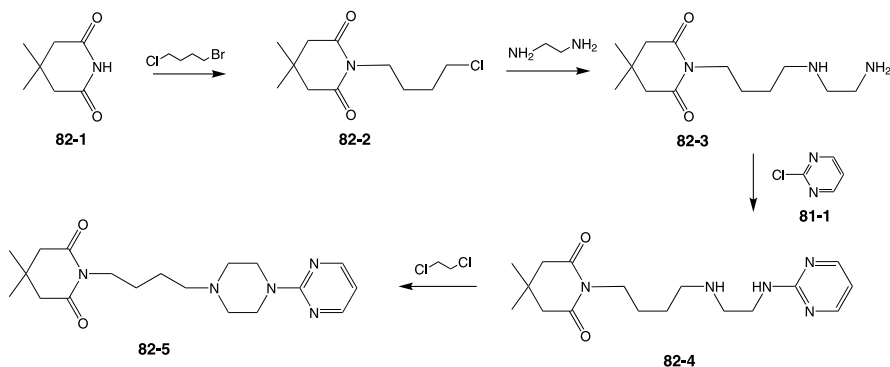
The reduction product (**83-1**) from Diels-Alder addition of maleimide and cyclopentadiene provides the starting material for yet another analogue. Reaction of the anion from that compound with propargyl chloride leads to alkylation on nitrogen and the formation of acetylene (**83-2**), a compound that now includes a reasonably acidic proton. The Mannich reaction provides the means for attaching the piperazine containing moiety as well as extending the connecting chain to the required four
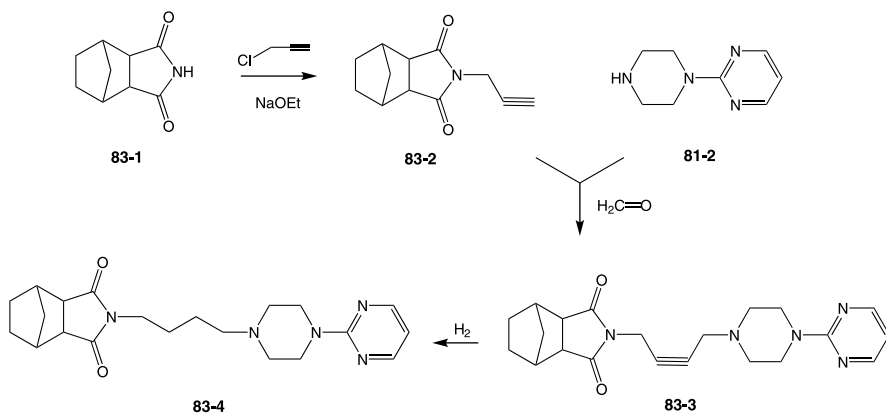
atoms. Thus, reaction of (83-2) with 2-pyrimidylpiperazine (81-2) and formaldehyde affords the intermediate (83-3). The acetylene group is then reduced by catalytic hydrogenation to afford **tandospirone (83-4)** [84].

A benzoisothiazole moiety can, interestingly, replace the terminal pyrimidine ring in this series. Reaction of thiosalicylic acid disulfide with thionyl chloride and then chlorine gives the dichloride (84-1); this is cyclized with ammonium hydroxide to give benzoisothiazolone (84-2), shown as its enol. The hydroxyl is then replaced with chlorine in the usual way with phosphorus oxychloride (84-3). The displacement of the newly introduced halogen by piperazine gives the mono-alkylation product (84-4). Alkylation of that intermediate with 1,4-dibromobutane then affords the spiro-cyclic quaternary salt (84-5) from double alkylation on the same amino group. Reaction of that intermediate with the anion from glutarimide (84-6) (from [81-6] and ammonia) leads to a ring opening and consequently alkylation on imide nitrogen; there is thus obtained **tiospirone (84-7)** [85].
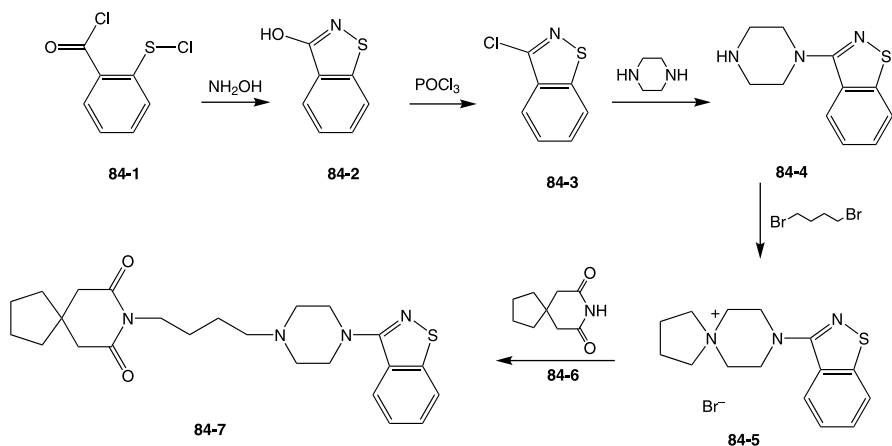
Compounds that inhibit HIV by binding to the specific receptor sites used by the virus to enter into the cells on the immune system cells, such as maraviroc (Chapter 8),
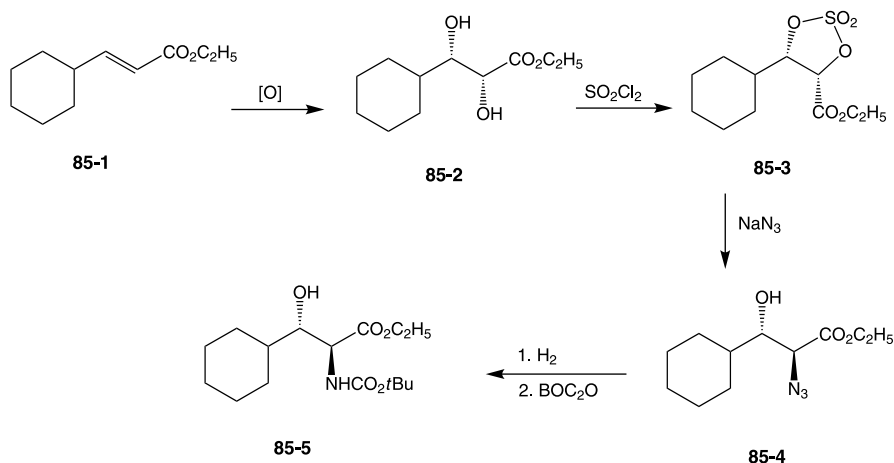
comprise one of the newer strategies for attacking the virus. The chemical structure of the inhibitor **aplaviroc** (**86-8**) that acts by the same mechanism is, however, quite different from that of its mechanistic counterpart. An enantioselective synthesis for the key starting amino acid starts with the oxidation of the double bond in cyclohexyl acrylic ester (**85-1**) with potassium osmate to afford the *cis* diol (**85-2**). Reaction of that intermediate with sulfuryl chloride affords the cylic sulfate ester (**85-3**). Treatment of that intermediate with sodium azide leads to an attack at the carbon bearing the carboxylate group with inversion of configuration (**85-4**). Catalytic reduction followed by reaction of the thus-formed amine with *tert*-butyloxycarbonic anhydride leads to the intermediate (**85-5**) as a single diastereomer [86].

In a three-component synthesis the amide (**86-1**) obtained from the ester (**85-5**) and benzyl isocyanide is reacted with the piperdone (**86-2**). The product from this transform consists of the addition product (**86-3**) where amide nitrogen in (**86-1**) as well as the carbon from the isocyanide have added to the carbonyl group on the piperidine. Treatment of the adduct (**86-3**) with a strong acid hydrolyzes the urethane function on the *tert*-butyloxycarbonic protecting group, leaving behind the primary
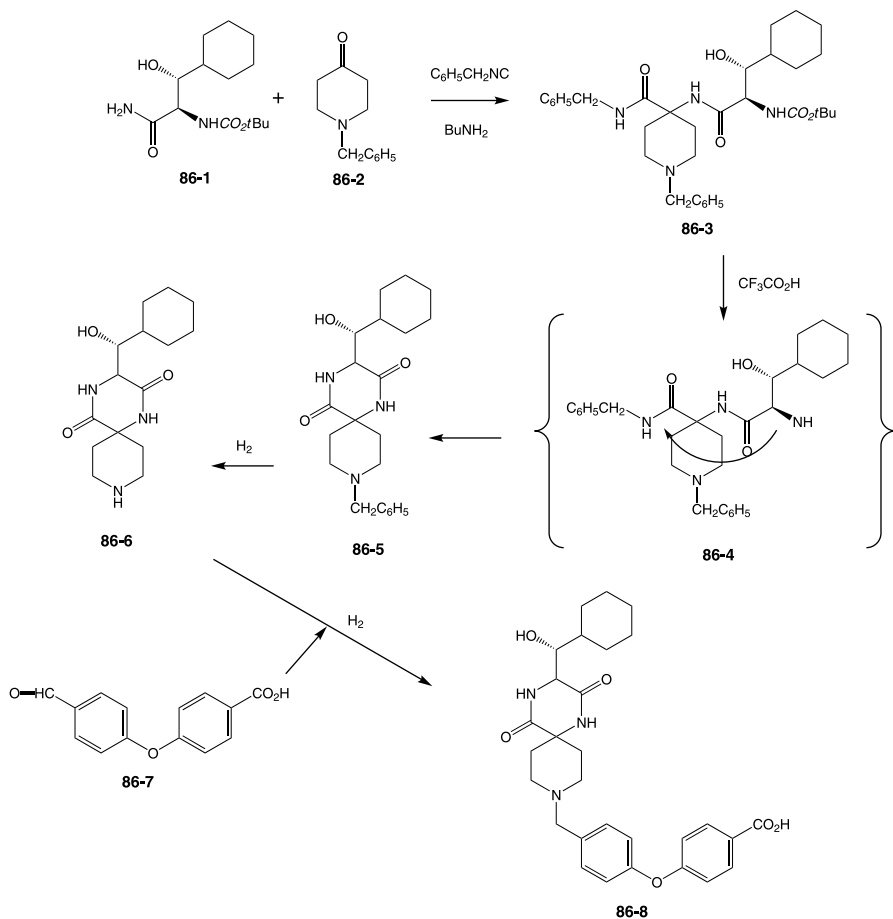
amine (**86-4**). That intermediate is not isolated but undergoes displacement of the benzyl amine function in an intramolecular amide exchange to form the diketo piperazine (**86-5**). Hydrogenation of this last product removes the benzyl protecting group to reveal the free piperidine (**86-6**). Reductive amination of (**86-6**) via the aldehyde group in the phenoxy acid (**86-7**) affords aplaviroc (**86-8**) [87].

9.3. RINGS CONTAINING THREE HETEROATOMS: THE TRIAZINES

The cytotoxic nucleosides that contain "unnatural" substituents such as **cytarabine** (**46-1**) have, as noted above, been used as antineoplastic agents. This activity may be enhanced by the incorporation of an additional nitrogen atom in that compound, turning the pyrimidine ring into a 1,3,5-triazine. The first step in the synthesis of one triazine-based agent consists of the standard glycosylation reaction of the triazine silyl ether (**87-2**) with the benzylated chloro arabinoside (**87-1**). Catalytic reduction of the product (**87-3**) leads to the removal of the benzyl protecting groups. The triazine ring in the product (**87-4**) is, however, partly reduced as well during that reaction. The sensitivity of the final compound precludes direct oxidation to restore the double bond. Instead, the compound is converted to the silyl ether (**87-5**); air oxidation followed by deprotection leads to the anti-tumor agent **fazarabine** (**87-6**) [88].
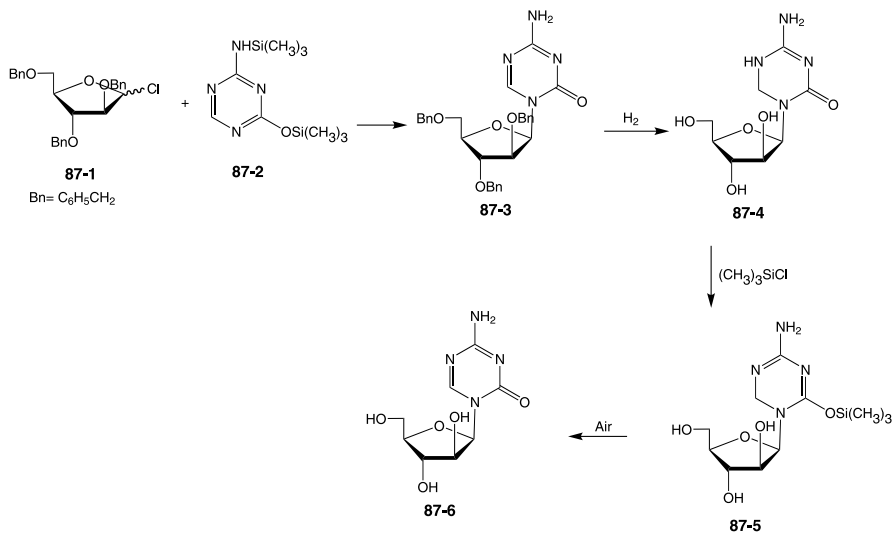
The route used to prepare the 3′-desoxy analogue relies on building the triazine ring onto the sugar. Thus, reaction of the benzoate protected chloro sugar (**88-1**) with silver isocyanate affords the displacement product (**88-2**), apparently mainly as the desired anomer. Condensation of that product with the O-methylurea (**88-3**) gives the product (**88-4**) from the addition of the urea amino group to the cumulene carbonyl. Treatment of that intermediate with ethyl formate completes the elaboration of the triazine ring, affording (**88-5**). Ammonolysis of the product both replaces the

ring methyl ether by an amino group and frees the hydroxyl groups by cleaving the benzoate esters. There is thus obtained the antineoplastic agent **decitabine (88-6)** [89].
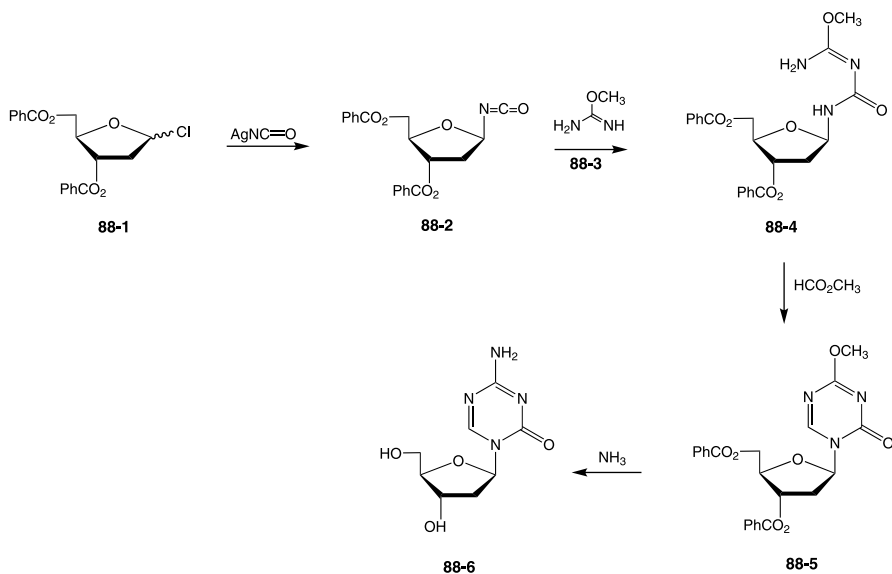
Pyrimidines have been extensively studied as a source for antibacterial and antiparasitic agents that act as folate reductase inhibitors (see, for example, **pyrimethamine [38-5]**). This activity is maintained in compounds that incorporate an additional ring of nitrogen. A partly reduced 1,3,5 triazine, **cycloguanil (89-4)**, shows
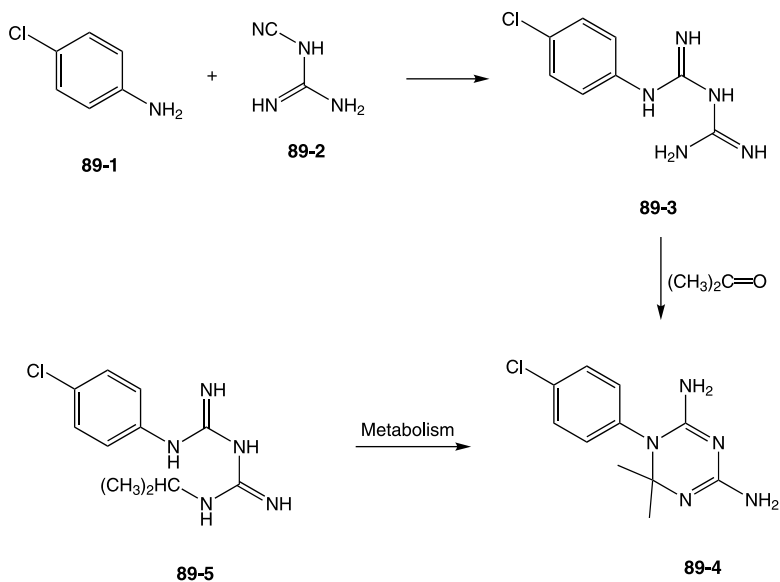
similar activity to the amino pyrimidines; the compound has been used as an antimalarial agent. The precursor to this drug was the open chain biguanide, **proguanil** (**89-5**), discovered in the course of a random screening study. Investigation of the metabolic fate of that compound revealed that the active agent was the oxidation product in which the methyne carbon on the isopropyl group had cyclized to form a triazine. That route for preparing the triazine synthetically starts by condensation of *para*-chloroaniline (**89-1**) with dicyanamide (**89-2**) to afford the biguanide (**89-3**). Reaction of that with acetone results in the formation of a cyclic aminal and thus **cycloguanil** (**89-4**) [90].

The breadth of the structural tolerance for the COX 2 inhibiting activity in 1,2-diaryl heterocycles [see celebrex, Chapter 8 (**31-5**), *et seq.*] is further illustrated by the fact that activity is maintained when the ring is expanded to a 1,2,4-triazine. The basic ring system (**90-2**) is obtained in a single step by reaction of the benzil (**90-1**) with semicarbazone. Reaction of the product with phosphorus oxychloride gives the corresponding chloro derivative (**90-3**). That halogen is then replaced by a methyl group by a reaction characteristic of heterocyclic systems. Thus, treatment of (**90-3**) with the ylide from methyl triphenylphosphonium bromide gives the phosphonium salt (**90-4**) product from the displacement of halogen by the anion on the methyl group. Hydrolysis of that intermediate leads to a loss of phosphorus as triphenylphosphine oxide and the consequent formation of **anitrazafen** (**90-5**) [91].
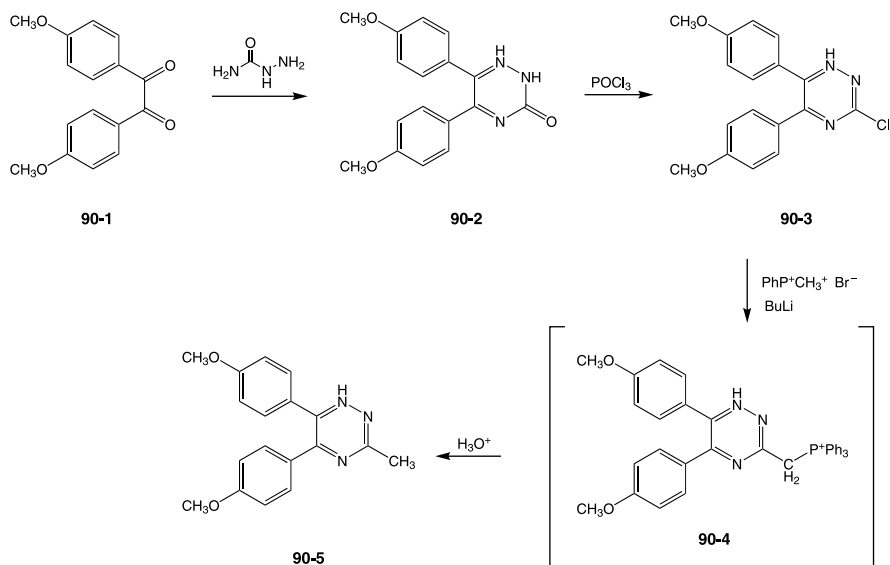
Preparation of the anticonvulsant agent **lamotigrine** (**91-3**) illustrates an alternate approach to 1,2,4-triazines. Condensation of acyl cyanide (**91-1**) with dicyanamide gives imine (**91-2**) as the initial product. Treatment of that intermediate with a base leads to the addition of the guanidino anion to the nitrile and thus the formation of the triazine ring [92].
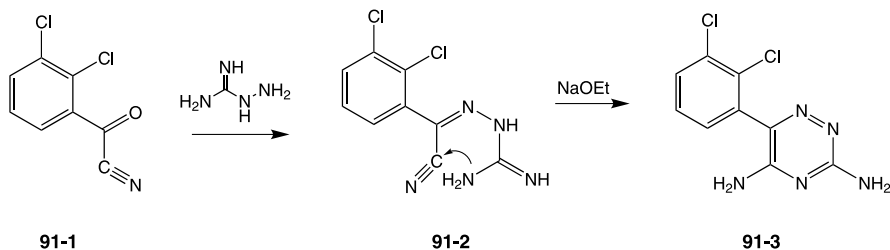
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CHAPTER 10

FIVE-MEMBERED HETEROCYCLES FUSED TO A BENZENE RING

10.1. COMPOUNDS THAT CONTAIN ONE HETEROATOM

10.1.1. Benzofurans

The bicyclic array in the few therapeutic agents based on the benzofuran ring plays the role of a rigid support for functional groups. As was also the case with the mono-cyclic furans, the ring system does not seem to form a pharmacophore.

One of the classical approaches to constructing the benzofuran ring involves aldol condensation of an ether of salicylaldehyde containing a β-carbonyl group. Thus, treatment of the ether (**1-1**) from alkylation of salicylaldehyde with chloroacetone with sodium ethoxide gives the acyl benzofuran (**1-2**). The carbonyl group is then removed by Wolff–Kishner reduction with hydrazine and potassium hydroxide to give (**1-3**). Aluminum chloride catalyzed acylation of the product with anisoyl chloride proceeds to give ketone (**1-4**); the methyl ether is then cleaved using pyridine hydrochloride to afford the phenol (**1-5**). Treatment of that compound with a basic mixture of iodine and potassium iodide leads to the iodination of the *ortho* positions and the formation of the coronary vasodilator **benziodarone** (**1-6**) [1].
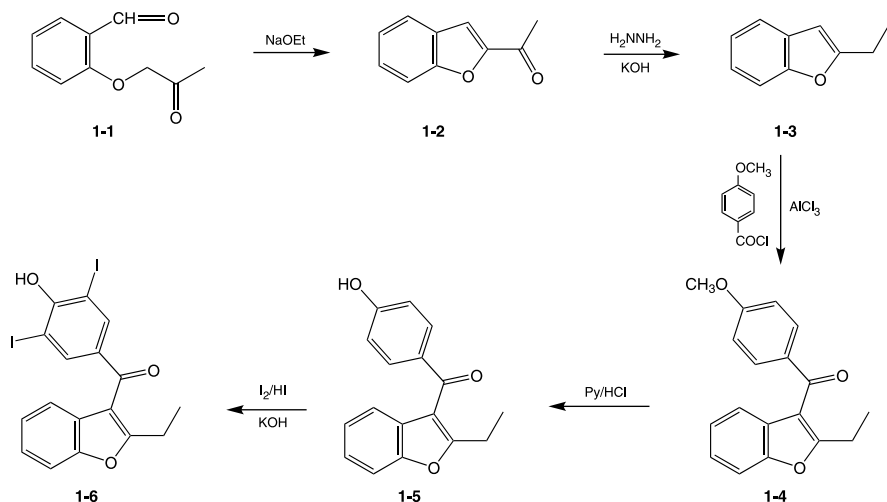
A recent halogen-free benzofuran that shares many structural features with its predecessor shows activity in controlling arrythmias. The synthesis starts with an unusual scheme for building the furan ring. Reaction of the benzyl bromide (**2-1**) with triphenylphosphine leads to phosphonium salt (**2-2**). Treatment of the salt with valeryl chloride in the presence of pyridine results in acylation on the now highly activated benzylic carbon (**2-3**). That product cyclizes to the benzofuran (**2-4**) on heating with expulsion of triphenylphosphine. Friedel–Crafts acylation of (**2-4**) with anisoyl chloride in the presence of stannic chloride proceeds on the
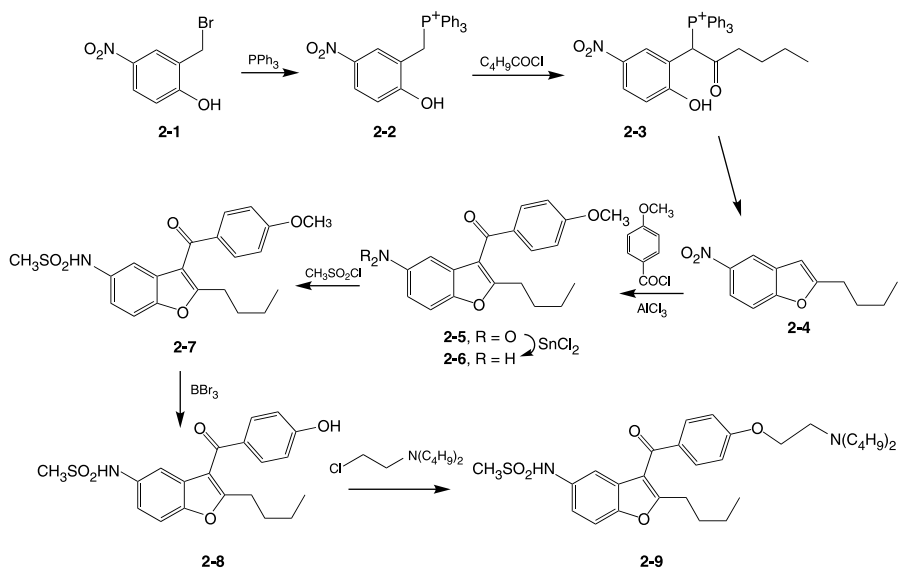
electron-rich furan ring to afford (**2-5**). The nitro group is next reduced with stannous chloride to give the amine (**2-6**). That newly formed amine is converted to the corresponding sulfonamide (**2-7**) by means of methanesulfonyl chloride. Reaction of this last product with boron tribromide cleaves the methyl ether, leading to the free phenol (**2-8**). Alkylation of that function with chloroethyl-dibutylamine in the presence of a mild base would then lead to the antiarrythmic agent **dronedarone** (**2-9**) [2].

The salicylaldehyde (**3-2**) required for the synthesis of a somewhat more complex benzofuran is obtained by acylation of phenol (**3-1**) with hexamethyelene tetramine (HMTA) in trifluoroacetic acid. It is likely that the reaction proceeds via an imino-formyl species formed by the dissociation of HMTA in the strongly acidic medium. The initially formed imine is hydrolyzed to the observed aldehyde (**3-2**) on workup. The benzofuran ring is formed, in this case, by reaction of (**3-2**) with ethyl bromomalonate in the presence of sodium ethoxide. The reaction can be visualized as proceeding to give first the displacement product (**3-3**); addition of the anion from this to the adjacent aldehyde will give the intermediate (**3-4**). The dicarboxylic acid formed when that product is saponified undergoes sequential decarboxylation and dehydration to afford the carboxylated benzofuran. There is thus obtained the platelet aggregation inhibitory **furagrelate** (**3-5**) [3].
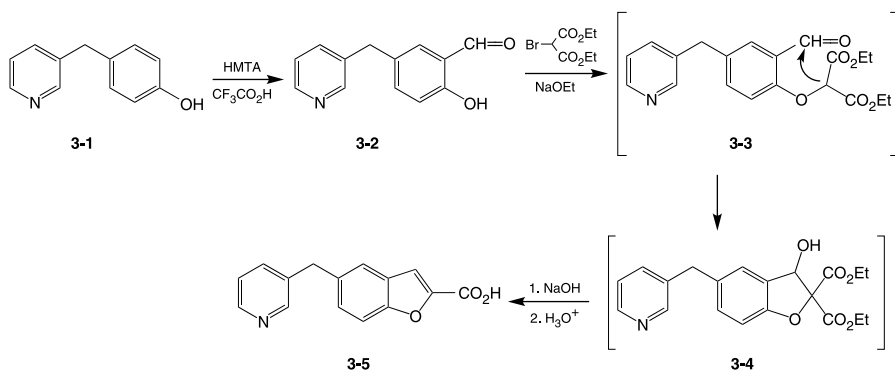
Substitution of a propionic acid fragment onto a benzofuran affords an NSAID "profen," illustrating yet again the flexibility of the SAR in this series. In this case, the benzofuran ring is prepared by an acid catalyzed cyclodehydration reaction. Alkylation of *ortho*-bromophenol (**4-1**) with phenacyl bromide (**4-2**) gives the corresponding ether (**4-3**). Treatment of that compound with polyphosphoric acid leads to the formation of the benzofuran (**4-4**). Reaction of that product with magnesium metal affords the corresponding Grignard reagent; addition of methyl pyruvate to the organometallic reagent leads to addition to the ketone and thus the formation of the tertiary carbinol (**4-5**). This is then dehydrated to the olefin by means of *para*-toluenesulfonic acid (**4-6**). The olefin is then reduced by means of catalytic hydrogenation. Saponification of the ester affords the NSAID **furaprofen** (**4-7**) [4].
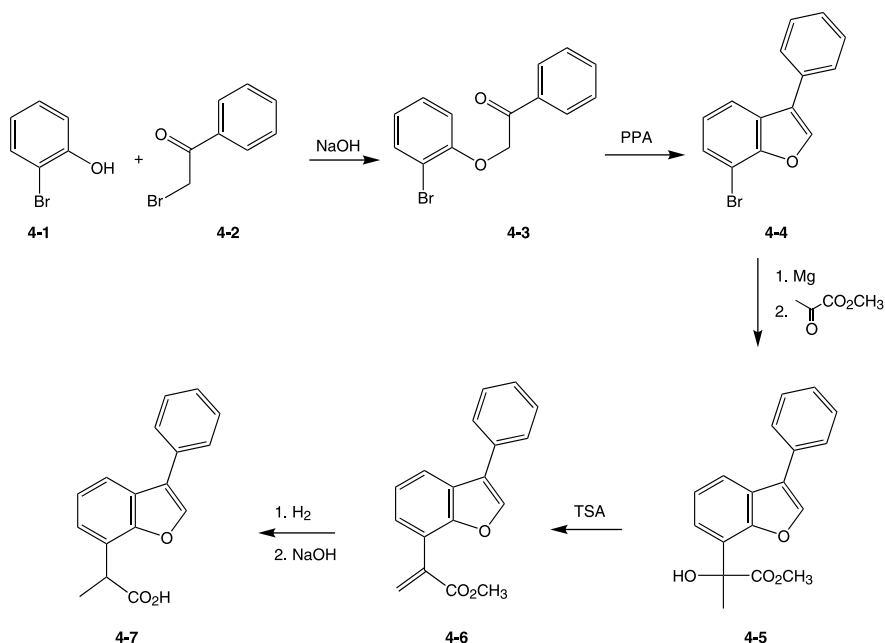
The fermentation product, **griseofulvin** (**5-6**), was the mainstay for the treatment of fungal infections until the discovery of the "conazoles" (see Chapter 8) and is in fact still currently in use for that indication. The drug is in all probability produced commercially by large-scale fermentation. A concise synthesis has, however, been developed; at least one drawback to its practical use is the fact that it produces racemic material while the natural product is chiral. Construction of the fragment (**5-3**) intended for the *spiro* ring involves first 1,2-addition of the lithium reagent from methoxyacetylene (**5-1**) to crotonaldehyde (**5-2**). The first-formed allylic alcohol is next oxidized to a ketone by means of manganese dioxide to give the Michael double acceptor (**5-3**). Preparation of the dihydrobenzofuran fragment starts with acylation of the highly substituted phenol (**5-4**) with chloroacetyl chloride in the presence of aluminum chloride. Treatment of the intermediate chloroketone with sodium acetate leads to internal alkylation; this leads to cyclization to the dihydrobenzo furan (**5-5**).
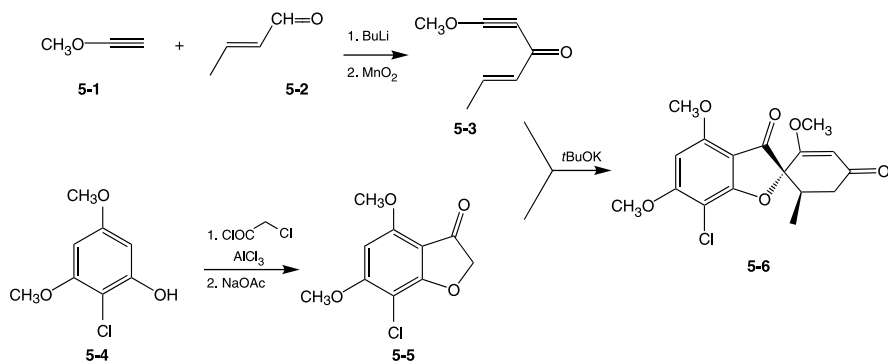
Reaction of that with potassium *tert*-butoxide affords the corresponding carbanion; this is thought to first add to the enone in (**5-3**). The anion from the reaction with a second equivalent of base then adds to the enone function to form the *spiro* ring. The fact that the product from this reaction has the same relative stereochemistry as the natural product is attributed to the better overlap of the enolate with the triple bond in the transition state leading to that isomer. The product from the reaction is thus ± **griseofulvin** (**5-6**) [5].

A series of antihypertensive agents based on antagonism of angiotensin II are described in Chapter 8 (see losartan (**77-4**) et seq.). A compound in which benzofuran replaces one of the benzene rings in biphenyl moiety found in the earlier series is itself a quite active antagonist. The synthesis of the substituted benzofuran moiety in the convergent scheme starts by reaction of the anion from (**6-1**) with tri-isopropyl borate to afford the boronic acid (**6-2**) on workup. Palladium catalyzed coupling with ethyl 2-bromobenzoate (**6-3**) then leads to the diaryl derivative (**6-4**). Trearment with bromine interestingly proceeds on the fused furan ring rather than the methyl group on benzene. That product is then saponified to afford carboxylic acid (**6-5**). Reaction of this last intermediate with diphenylphosphinous azide in *tert*-butanol leads to the equivalent of the Curtius rearrangement. The first-formed isocyanate adds solvent to give the urethane (**6-6**). A second exposure to bromine this time proceeds on the benzylic carbon to afford the substituted benzofuran (**6-7**).
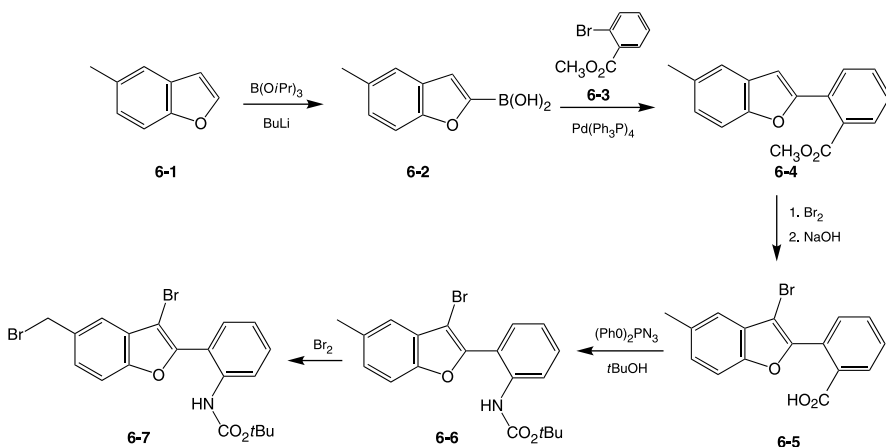
The second arm of the scheme involves first a reaction of the β-beta ketoester (**7-1**) with nitrous acid. The first product from nitrosation on the activated carbon spontaneously rearranges to afford oxime (**7-2**). Treatment with acetyl chloride then affords the *O*-acylated oxime (**7-3**). Condensation of that compound with the imino ether from propionitrile leads to the formation of the imidazole (**7-4**).
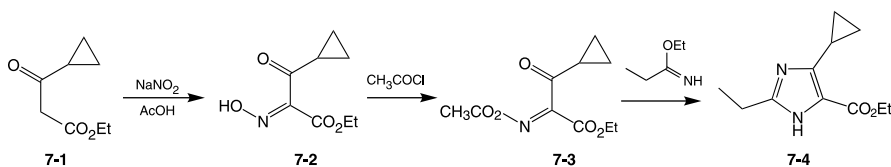
Reaction of the imidazole (**7-4**) with the benzofuran derivative (**6-7**) leads to the displacement of the benzylic halogen and the formation of the alkylation product (**8-1**). Treatment of that intermediate with trifluoroacetic acid breaks open the urethane to afford the corresponding free amine. This is allowed to react with triflic anhydride to afford the trifluoromethyl sulfonamide (**8-2**). The ester group on the imdidazole is then saponified, and the newly formed acid is reacted with carbonyl diimidazole. Reaction with ammonia converts the activated carboxyl group to the amide. There is thus obtained the angiotensin antagonist **saprisartan** (**8-3**) [6].
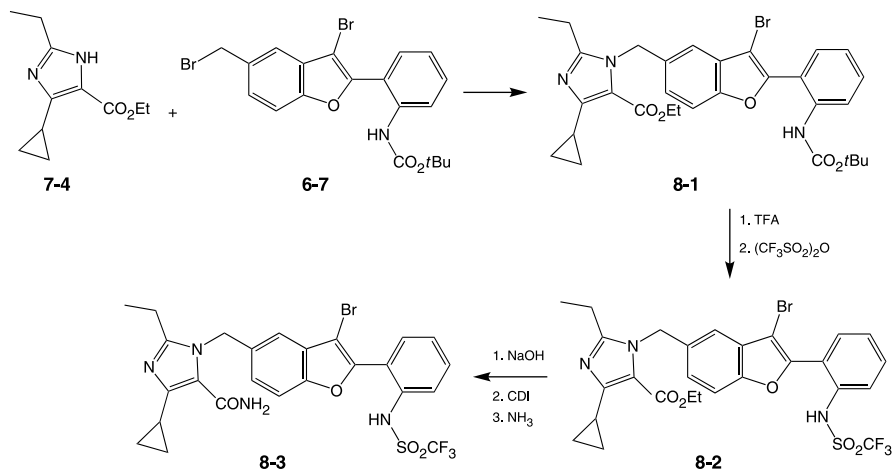
A benzoisofuran provides the nucleus for the SSRI antidepressant **citalopram** (**9-8**). Condensation of the phthalide (**9-1**) with the Gignard reagent (**9-2**) from 4-bromofluorobenzene leads to addition to the carbonyl group to afford the ring opened hydroxyketone (**9-3**). Addition of a single organometalic group to the phthalide
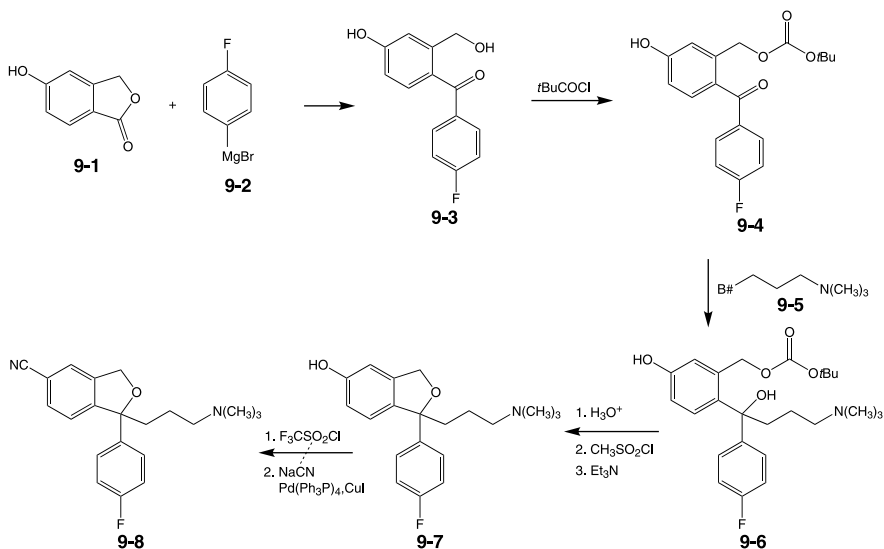
may be attributable to the stability of the first-formed addition complex. The benzylic hydroxyl group is next converted to its *tert*-butoxycarbonyl derivative (**9-4**). Condensation of that intermediate with a second Grignard reagent, this one from 3-chloropropyl dimethylamine (**9-5**), leads to the addition product (**9-6**). The reason for the specificity for the ketone over the carbonate may be due to the sterically crowded condition about the latter. Treatment with acid then removes that protecting group. Reaction of the free alcohol with methanesulfonyl chloride forms the mesylate of the primary alcohol. Exposure to triethylamine leads to the displacement of that function by the adjacent tertiary hydroxyl group and thus closure to the isobenzofuran ring (**9-7**). The phenolic hydroxyl is then converted into a leaving group, in this case a triflate, by acylation with trifluoromethyl sulfonyl chloride. Reaction of this last with sodium cyanide, in the presence of triphenylphosphine:palladium and cuprous iodide, replaces the triflate by cyanide. There is thus obtained the antidepressant compound citalopram (**9-8**) [7].

10.1.2. Indoles

The relative abundance of indole-based therapeutic agents is attributable only in part to the fact that this nucleus forms part of a pharmacophore for selected CNS agents. The indole moiety, however, likely simply serves as a rigid bicyclic support in the majority of the agents discussed below.

An indole prepared in the late 1960s at that time showed unexpected activity against various models of inflammation. This was surprising since the compound was quite devoid of the acidic proton then considered necessary for NSAID activity. Though the agent failed to reach the clinic due to toxicity, it can be considered to be the intellectual forerunner for what would several decades later become a sizeable series of COX-2 inibitors [8]. The Fischer indole synthesis comprises the key reaction for the preparation of this agent and several of those that follow (see reference [9] for a review). In a broad outline, the first step in this quite complex transform involves first the formation of a hydrazone from an aryl hydrazine and a carbonyl derivative of the fragment that is to form the fused heterocyclic ring. Protonation of one of the nitrogens accompanied by migration of the *N,N'* double bond forms a species such as (**10-1**). This then undergoes an electrocyclic rearrangement in which the carbon α of the hydrazone bonds to the *ortho* position of the aromatic ring with scission of the relatively weak *N,N* hydrazine bond to form the *bis*-imine (**10-2**). The ring imine then adds to its side chain counterpart to give the fused indoline (**10-3**). (The direction of this reaction is not crucial since reverse addition should lead to the same overall product.) Loss of the elements of ammonia leads finally to an indole (**10-4**).
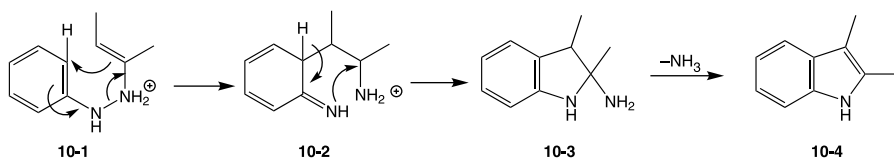
Reaction of desoxyanisoin (**11-1**) with phenylhydrazine goes in a straightforward manner to hydrazone (**11-2**). Treatment of that intermediate with acetic acid leads to the formation of the indole ring and the formation of **indoxole** (**11-3**) [10].
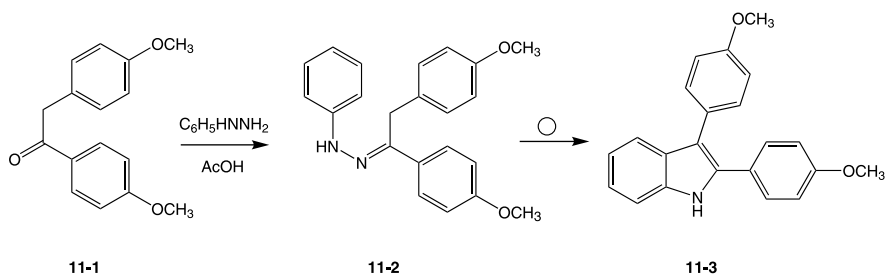
A simple indole derivative, serotonin (5-hydroxytriptamine; 5-hydroxy-3-β-aminoethylindole, 5HT (**13-1**), is an important neurotransmitter in the brain. A variety of mental diseases and in particular depression have been traced to inappropriate levels of receptor sensitivity to this compound. The 5-hydroxytriptamine moiety has thus been used in the design of CNS drugs in an attempt to insure interaction with brain receptors. Condensation of dimethoxy phenylhydrazine (**12-1**) with the product (**12-2**) from alkylation of 4-(2-methoxyphenyl)piperazine with 3-bromopropyl methyl ketone gives the hydrazone (**12-3**). Treatment of that intermediate with hydrogen chloride leads to rearrangement to an indole and the formation of the antipsychotic agent **milipertine** (**12-4**) [11], a compound that shares both the oxygen at position 5 and an ethylamino side chain at position 3 with serotonin.
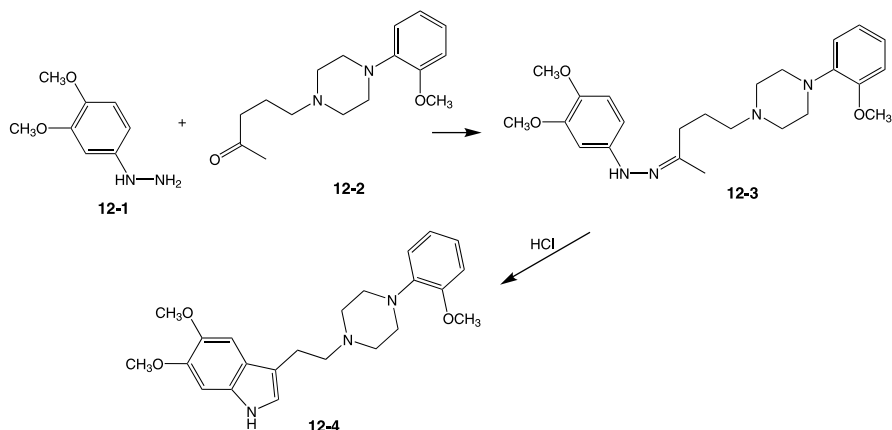
The term migraine headache is something of a misnomer in that an attack involves syndromes that go beyond those of an ordinary pain in the head. Attacks differ further in the fact that they are quite resistant to the common headache remedies such as aspirin. Close study revealed the fact that migraine attacks are closely associated with fluctuating levels of the indole neurotransmitter serotonin in peripheral brain nerve cells. The finding that activity against migraine of the ergot derivative

methysergide was due to its interaction with serotonin receptors led to the finding of a series of indole-based compounds with more specific affinity for those receptors. The first of these compounds, **sumatriptan** (**13-8**), can be viewed as a 5HT in which the acidic phenol group in the neurotransmitter is replaced by a comparably acidic sulfonamide with an interposed methylene group; it differs further by the methyl groups on the terminal side chain amine. The preparation starts by conversion of the aniline (**13-2**) to its diazonium salt with nitrous acid; reduction with stannic chloride then affords the corresponding arylhydrazine (**13-3**). Condensation with 3-cyanopropionaldehyde (**13-4**) gives the hydrazone (**13-5**). Treatment of that product with hydrogen chloride leads to rearrangement to the indole (**13-6**). The nitrile is then reduced to the primary amine by catalytic hydrogenation (**13-7**). Reaction of the amine with excess formalin and sodium borohydride results in the formation of the *N,N*-dimethylated derivative, yielding **sumatriptan** (**13-8**) [12].
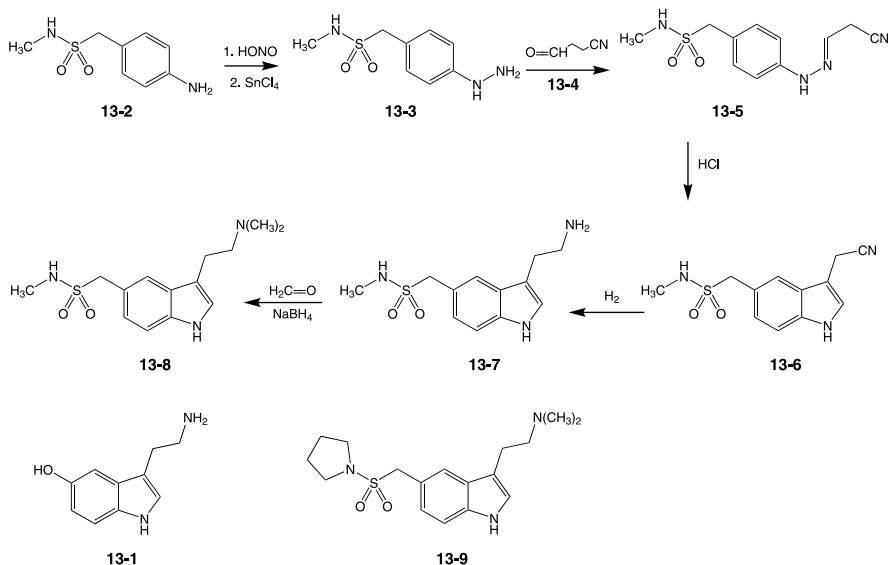
Subsequent research revealed that the group on the benzene ring need not be included as an ionizable proton. The analogue lacking that feature, **almotriptan**, (**13-9**), prepared by the same scheme but substituting a pyrrolidylsulfonamide for (**13-2**) [13] shows much the same activity as its forerunner. The scheme used for preparing the compound that bears a methyltriazole group at position 5 illustrates an alternate indole synthesis. Reaction of 4-nitrobenzyl bromide (**14-1**) with 1,2,4-triazole (**14-2**) results in the displacement of halogen and the formation of an alkylation product (**14-3**). Catalytic hydrogenation then reduces the nitro group to the corresponding aniline (**14-4**). Treatment of that intermediate with iodine monochloride leads to the iodination of the position adjacent to the amino group and the formation of (**14-5**). In the key reaction, palladium-catalyzed coupling of silytated 1-butyn-4-ol (**14-6**) probably leads initially to the formation of the adduct (**14-7**)

reaction at the 2 position of the acetylene. Internal displacement of the silyl protecting group by the basic aniline leads to the formation of the indole (**14-8**). Treatment of the product with acid removes the remaining silyl group. The resulting alcohol is then converted to a mesylate leaving group (**14-9**) with methanesulfonyl chloride. Displacement of the mesylate with dimethylamine completes the synthesis of **rizatriptan** (**14-10**) [14].
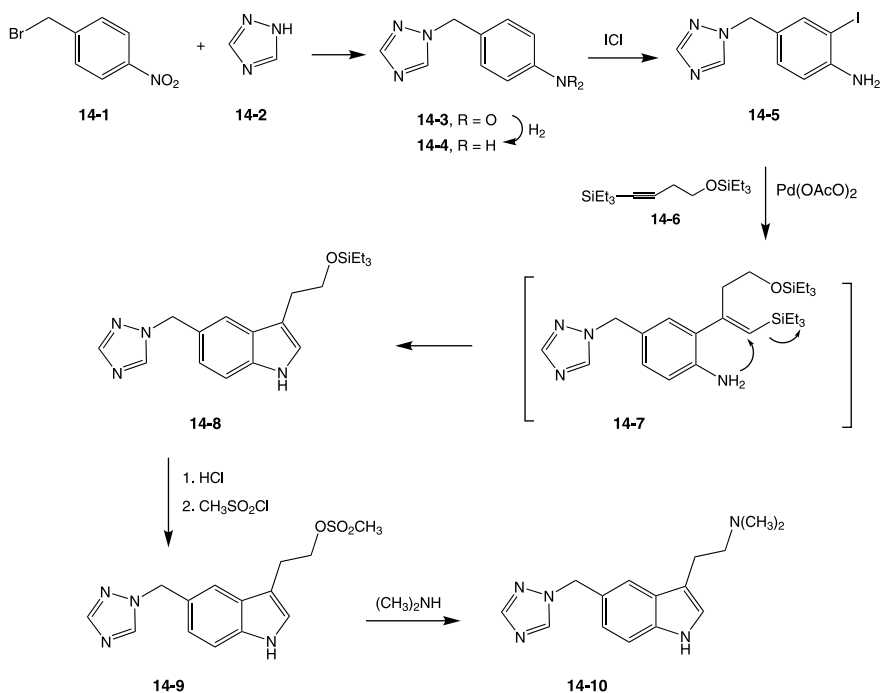
The synthesis of a "triptan" with a chiral side chain begins by reduction of the carboxylic acid in chiral 4-nitrophenylalanine (**15-1**). The two-step procedure involves conversion of the acid to its ester by the acid chloride by successive reaction with thionyl chloride and then methanol. Treatment of the ester with sodium borohydride then afford the alanilol (**15-2**). Reaction of this last intermediate with phosgene closes the ring to afford the oxazolidone (**15-3**); the nitro group is then reduced to the aniline (**15-4**). The newly obtained amine is then converted to the hydrazine (**15-5**). Reaction of this product with the acetal from 3-chloropropionaldehyde followed by treatment of the hydrazone with acid affords the indole (**15-6**). The terminal halogen on the side chain is then replaced by an amine by successive displacement by means of sodium azide followed by catalytic reduction of the azide. The newly formed amine is then methylated by reductive alkylation with formaldehyde in the presence of sodium cyanoborohydride to afford **zolmitriptan** (**15-7**) [15].
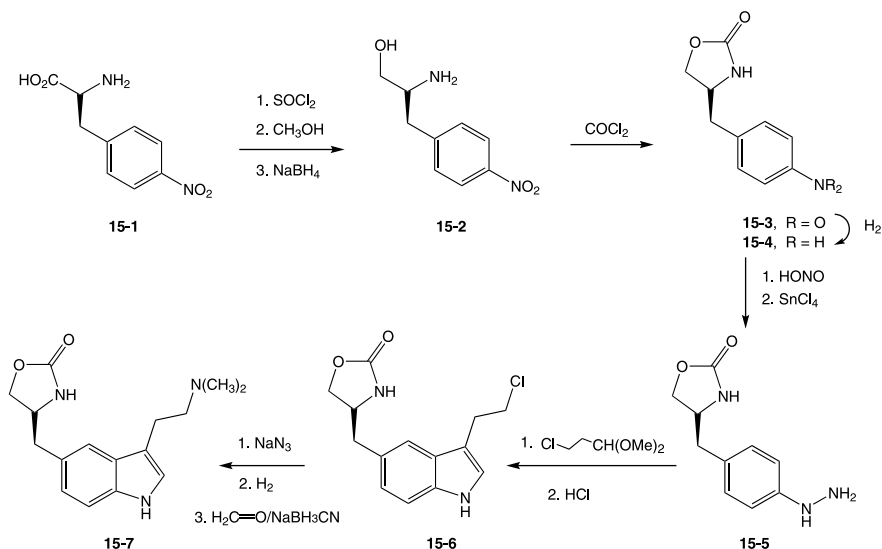
The side chain on the fused five-membered ring can, interestingly, form part of a piperidine or piperazine ring. The scheme for preparing the first of these takes advantage of the reactivity of the indole 3 position. The relatively weak base, sodium hydroxide, thus catalyzes the addition of bromoindole (**16-1**) to the carbonyl group in 4-*N*-methylpiperidone (**16-2**) to afford carbinol (**16-3**). This product dehydrates in the presence of acid; catalytic reduction of the thus-produced olefin then affords the
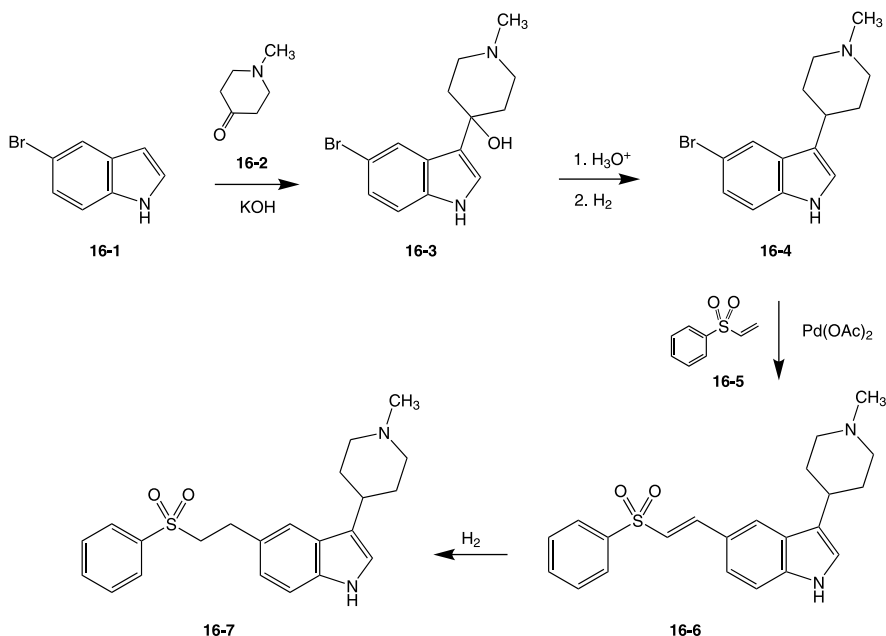
piperidyl derivative (**16-4**). Coupling of this intermediate with vinyl sulfone (**16-5**) leads to the product of displacement of bromine at position 5 (**16-6**). Catalytic reduction of the side chain unsaturation then affords the anti-migraine agent **naratriptan** (**16-7**) [16].

Activity is retained when the side chain bearing basic nitrogen is extended by an additional carbon. Synthesis of the substituted pyrimidine for the side chain starts with the condensation of dimethyl glyoxylate (**17-1**) with guanidine to afford the pyrimidol (**17-2**). The hydroxyl group is then replaced by a leaving group, in this case chlorine, by reaction with phosphorus oxychloride. The product from that reaction (**17-3**) is then alkylated with *N*-carbethoxy piperazine (**17-4**) to afford (**17-5**). Treatment with acid removes the protecting group to afford piperazine (**17-6**), an intermediate suitable for alkylation. Preparation of the indole portion of the molecule begins with the two-step conversion (diazotization then reduction) of aniline (**13-3**) to the corresponding hydrazine. Heating that intermediate with ω-chlorovaleraldehyde, itself prepared in two steps from tetrahydropyran, in the presence of acid leads directly to the indole (**17-7**) that has in place the requisite side chain link. Subsequent alkylation of piperazine (**17-6**) with (**17-7**) leads to the serotonin antagonist **avitriptan** (**17-8**) [17].
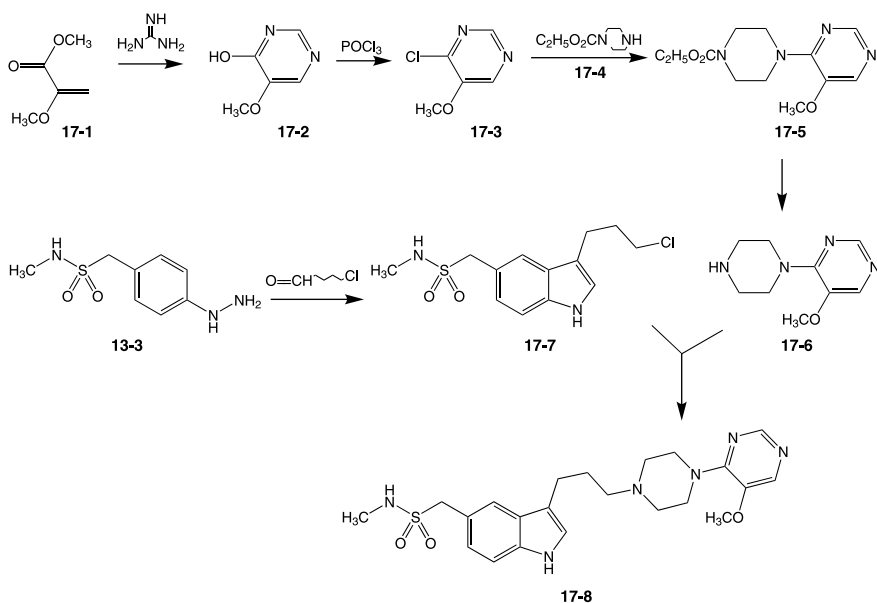
The Fischer indole synthesis is quite tolerant of additional functional groups in the starting material. Thus reaction of 4-dimethylaminocyclohexanone (**18-2**) with phenylhydrazine (**18-1**) in acetic acid leads directly to **cyclindole** (**18-3**) [18], a compound described as an antidepressant. A slightly different approach is used to prepare the fluorinated analogue. The tricylic indole (**18-5**), in this case, is obtained by reaction of 2,4-difluorophenylhydrazine (**18-4**) with 4-hydroxy-cyclohexanone. The hydroxyl
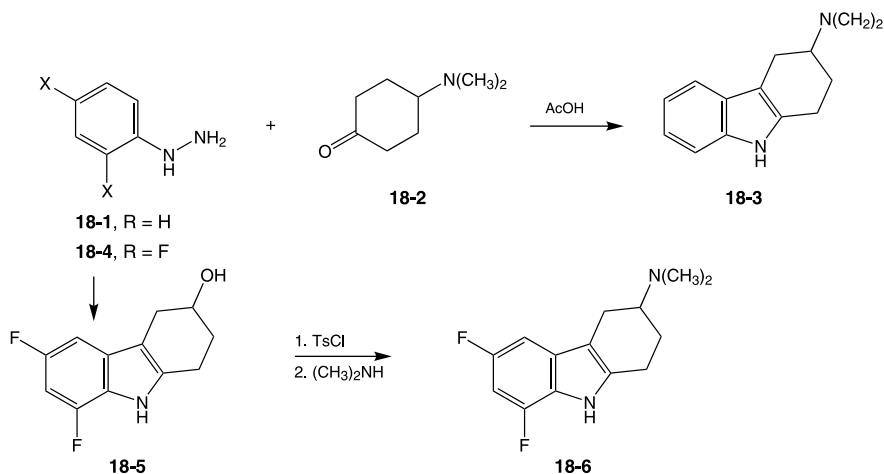
group in the product, (**18-5**) is then converted to its tosylate by reaction with *para*-toluenesulfonyl chloride. Displacement with dimethylamine then yields the antipsychotic agent **flucindole** (**18-6**) [19].

The side effects frequently observed on prolonged use of antipsychotic drugs that act on dopamine receptors have been ascribed to indiscriminate antagonism at sites
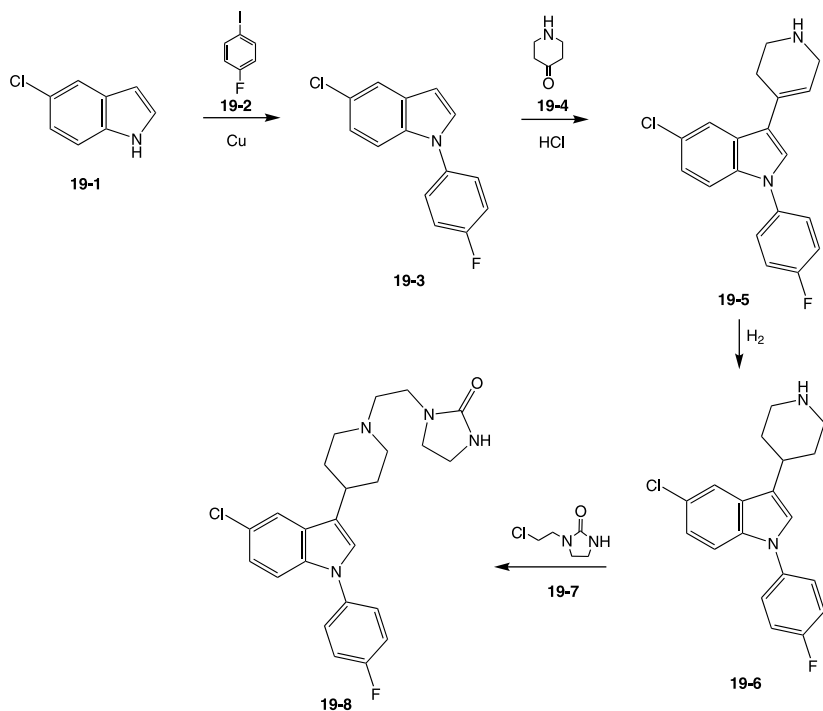
outside the brain. Replacement of one of the benzene rings in those drugs by an indole leads to agents that have greater specificity for the dopamine D2 receptors associated with psychoses. The synthesis of the indole-based dopamine antagonists **sertindole** (**19-8**) starts with copper-catalyzed Ulman coupling of 4-fluoroiodobenzene (**19-2**) to afford the alkylated indole (**19-3**). Condensation of that intermediate with piperidone (**19-4**) invokes the enamine-like character of the indole 3 position to afford the product from addition to the carbonyl group. The hydroxyl in the first-produced dehydrated product under the acidic conditions affords the olefin (**19-5**); the double bond is then reduced by catalytic hydrogenation (**19-6**). Alkylation of the piperdine with the side chain reagent (**19-7**) that occurs in a number of other antipsychotic drugs then affords **sertindole** (**19-8**) [20].

Indomethacin (**20-1**) constitutes one of the first and most potent NSAIDs discovered in the second part of the twentieth century. One of the many syntheses for this drug illustrates the versatility of the classic indole synthesis. Thus, condensation of the chlorobenzoyl arylhydrazide (**20-1**) with levulinic acid (**20-2**) leads to the hydrazone (**20-3**). This rearranges to indole (**20-4**) on treatment with a strong acid [21].
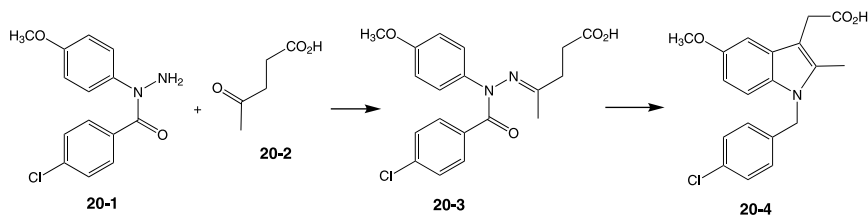
A fused tricyclic ring system based on an indole provides yet another NSAID. Michael addition of the anion from diethyl methylmalonate to cyclohexanone followed by acid hydrolysis of the product gives cyclohexanone (**21-3**), which incorporates the characteristic "profen" 2-substituted carboxylic side chain. Sequential reaction with *para*-chlorophenylhydrazine and a strong acid gives the fused indole
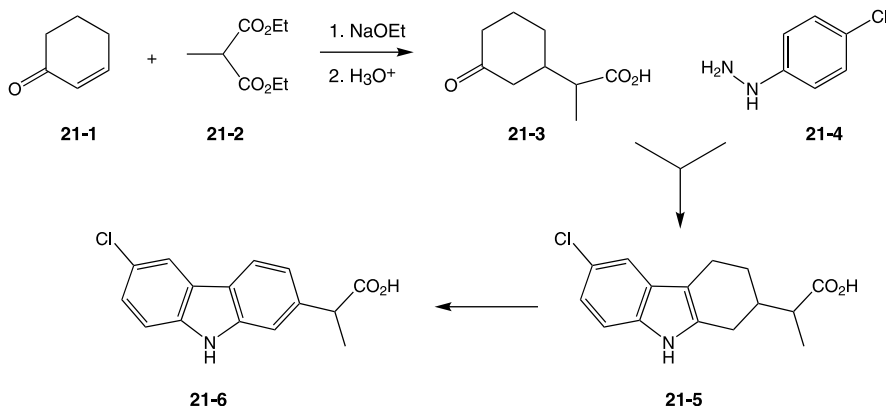
derivative (**21-5**). The carboxylic acid group is then esterified and the cyclohexane ring aromatized by some unspecified means. Saponification of the ester gives the free acid and thus affords **carprofen** (**21-6**) [22].

The substrate arachidonic acid, which often leads to the formation of inflammatory prostaglandins, is stored in tissues as one of a number of phospholipids; these, as the name indicates, comprise complex phosphate containing esters. The anti-inflammatory corticosteroids inhibit the action of the enzyme, phospholipase A2, that frees arachidonic acid. Inhibition of that enzyme would be expected to depress levels of inflammatory prostaglandins at their very inception. A highly substituted indole derivative has shown good activity as a phospholipase A2 inhibitor. Alkylation of the anion from the treatment of indole (**22-1**) with benzyl chloride affords the corresponding N-benzylated derivative (**22-2**). The methyl ether at the 4 position is then cleaved by means of boron tribromide (**22-3**). Alkylation of the enolate from reaction of the phenol with sodium hydride with *tert*-butyl bromoacetate affords the corresponding O-alkyl product (**22-4**). Reaction of this last intermediate with oxalyl chloride proceeds on the only open position of the heterocyclic ring to give the acylated derivative (**22-5**) as its acid chloride. Treatment of this last with ammonia gives the corresponding amide. The *tert*-butyl ester is then cleaved with acid to afford the phospholipase inhibitor **varespladib** (**22-6**) [23].
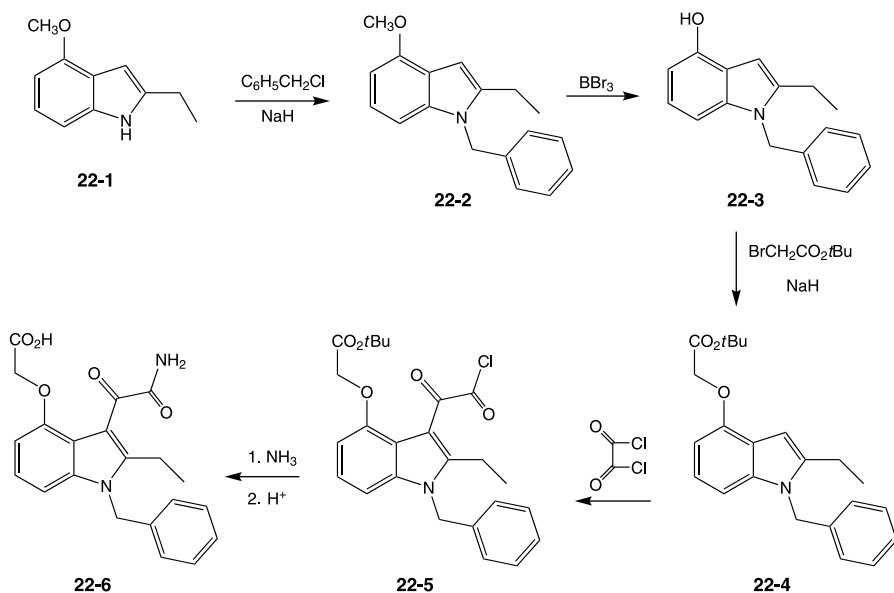
Yet another indole-based lipoxygenase inhibitor has shown activity in models of inflammatory bowel disease. The starting benzylaniline (**23-3**) can speculatively be obtained by alkylation on the phenol oxygen in (**23-2**) with 2-bromomethylquinoline (**23-1**). The customary diazotisation reduction sequence then affords the

corresponding hydrazine (**23-4**). Bromomethyl keto-ester (**23-5**) is then allowed to react with *tert*-butylmercaptan in a convergent scheme to afford the intermediate (**23-6**). Condensation of the hydrazine (**23-4**) with keto-ester (**23-6**) in the presence of acid proceeds to form the indole. Saponification of the ester then affords **quifaplon** (**23-7**) [24].
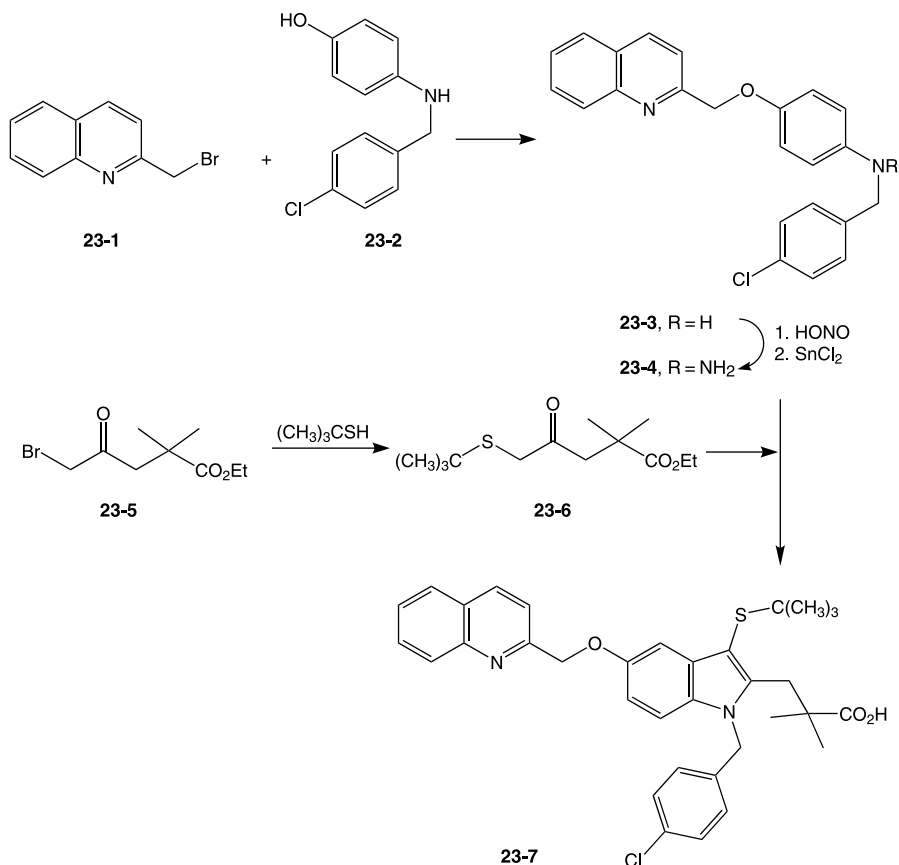
The structures of most antiallergic antagonists of leukotrienes terminate in a carboxylic aid that duplicates that in the endogenous product. This function is replaced by an acyl-sulfonamide in the idole-based antagonist **zafirlukast** (**24-8**). The 3 position on indoles is quite reactive toward electrophiles as a consequence of its partial enamide-like character. Silver oxide catalyzed alkylation of the nitroindole (**24-1**) with the benzyl bromide (**24-2**) proceeds to afford the product from coupling at the indole 3 position (**24-3**). The proton on nitrogen is then removed with sodium hydride; treatment of the anion with methyl iodide then yields the *N*-methylated derivative. The nitro group is then reduced by catalytic hydrogenation to the aniline (**24-4**). Acylation of the newly formed amine with cyclopentyl chloroformate (**24-5**)

gives the urethane (**24-6**). The benzoate methyl ester is then selectively cleaved with lithium hydroxide in DMF. Coupling of that product with *ortho*-tolysulfonamide (**24-7**) gives the corresponding acyl sulfonamide. There is thus obtained **zafirlukast** (**24-8**) [25].
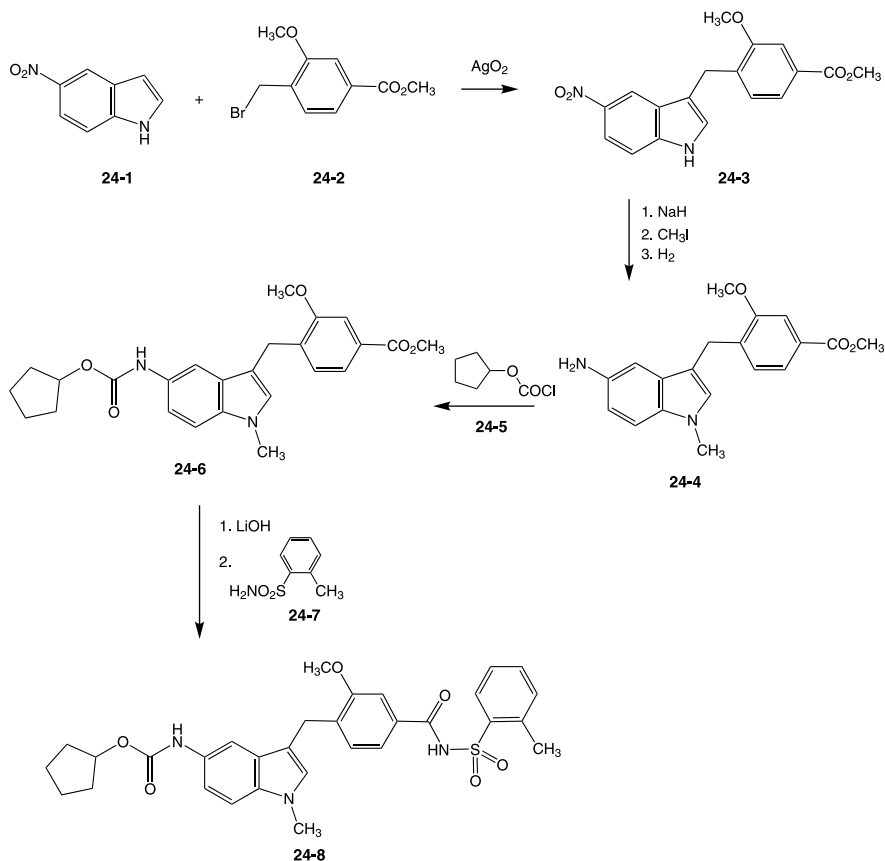
As a further illustration of the reactivity of the 3 position toward electrophiles, the methoxyindole (**25-1**) readily undergoes Mannich reaction with formaldehyde and dimethylamine to afford the aminomethylated derivative (**25-2**). Treatment of that intermediate with potassium cyanide leads to the displacement of dimethylamine and the formation of the nitrile (**25-3**), possibly by an elimination-addition sequence involving a 3-exomethylene-indolenine intermediate. The protons on the methylene group adjacent to the nitrile are quite acidic and readily removed. Reaction of (**25-3**) with methyl carbonate in the presence of sodium methoxide gives the carbomethoxylated derivative (**25-4**). Catalytic hydrogenation leads to reduction of the nitrile to a primary amine. There is thus obtained the antihypertensive agent **indorenate** (**25-5**) [26].
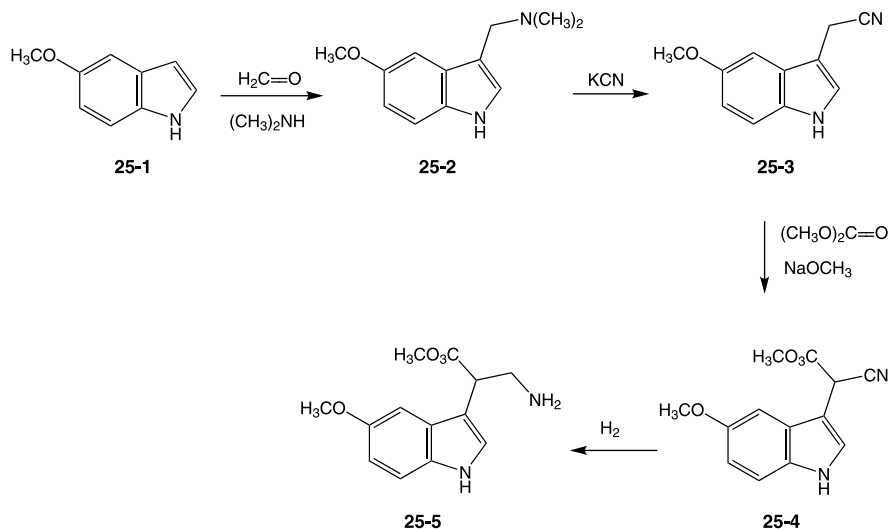
The introduction of the fungal metabolite **lovastatin** (**26-9**) has led to a sizeable class of clinically effective cholesterol lowering drugs. These agents, known familiarly as the "statins," block an enzyme, HMG-CoA reductase, that is involved in the synthesis of mevalonate, an early precursor of cholesterol. Extensive work has
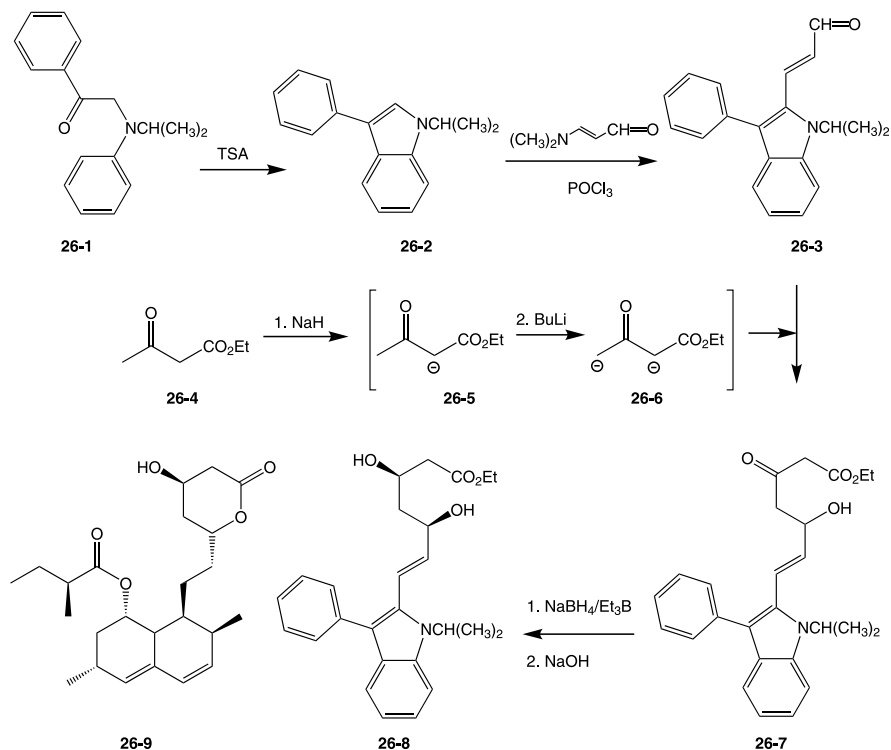
demonstrated that the mevalonate-like lactone ring, or its ketoacid precursor, is essential for activity; considerable structural freedom exists as to the nature of the remainder of the molecule. The nonchiral synthesis of an indole-based analogue starts with a different strategy than those heretofore described for forming the indole ring. Thus, cyclodehydration of the alkylation product (**26-1**) from *N-iso*-propylaniline with phenacyl bromide with toluenesulfonic acid affords the indole (**26-2**). The side chain is added to the only remaining open position on the heterocyclic ring by what may be viewed as a vinylogous Villsmeyer reaction. Thus, treatment of (**26-2**) with 3-dimethylaminoacrolein and phosphorus oxychloride gives the substituted acrolein (**26-3**) on workup. The side chain is then extended by addition of the more nucleophilic terminal enolate of the acetoacetate dianion (**26-6**) obtained by sequential reaction of ethyl acetoacetate with sodium hydride (**26-5**) and then butyl lithium (**26-6**). This doubly charged species affords the chain extended product (**26-7**) on reaction with (**26-3**). The newly introduced carbonyl group is then reduced with a mixture of sodium borohydride and triethyl borane to give the diol in which the hydroxyls bear the desired relative configuration. Saponification of the ester group leads to the acid racemic **fluvastatin** (**26-8**) [27], isolated as its sodium salt. It should be noted, however, that the commercial drug consists of a single enantiomer.

10.1.3. Indolines and Isoindolines

Partly reduced counterparts of the indole nucleus provide the basis for several agents with varied biological activities. A pair of closely related *N*-phenyl derivatives have both shown antidepressant activity in test systems. The apparent preference for the monomethyl amine suggests that these act by the same mechanism as the classical tricyclic antidepressants, where the secondary amine is the more active species. The first step in the preparation of the common intermediate (**27-3**) to these compounds consists of acylation of diphenylamine (**27-1**) with chloroacetyl chloride.
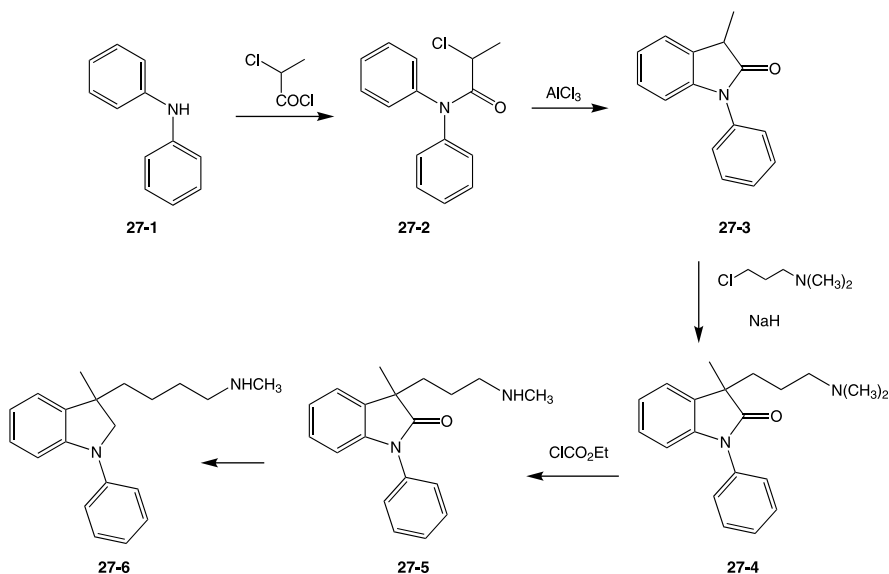
Cyclization of the product (**27-2**) under Friedel–Crafts conditions gives the desired indolinone (**27-3**). Reaction of the carbanion obtained on treatment of that with 3-chloropropyldimethylamine then gives the alkylation product (**27-4**). It should be noted that, in spite of this extra step, the scheme is greatly simplified by starting with the very readily available tertiary amine. The superfluous methyl group is then removed by reaction of (**27-4**) with ethyl chloroformate in the current version of the Von Braun reaction. There is thus obtained **amedalin** (**27-5**). Reduction of the amine by any of several methods, for example diborane, leads to the antidepressant **daledalin** (**27-6**) [28].

The conventional NSAIDs noted thus far rely on a carboxylic acid for the required acidic proton. This function can, however, also be supplied by a highly activated enolic system; the prototype **piroxicam** and its analogues are discussed in more detail in Chapter 11. Another highly enolizable compound based on the indolone nucleus displays similar activity. The preparation begins with conversion of indolone (**28-1**) to its carbamate (**28-2**) by successive conversion to the urethane by treatment with ethyl chloroformate and then ammononlysis of that intermediate. The extra electron withdrawing power of the newly introduced function apparently increases the acidity of the benzylic methylene group sufficiently so that it can be removed with 2,6-dimethylaminopyridine (DMAP). Reaction of (**28-2**) with 2-carbethoxythiophene (**28-3**) in the presence of that catalyst gives the β-dicarbonyl condensation product **tenidap** (**28-4**) [29], shown as one of the enol tautomers.
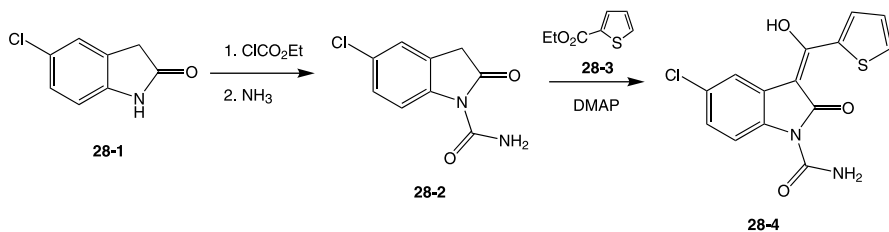
Solid tumors are highly dependent on the growth of new blood vessels, a process termed neoangiogenisis, which provide oxygen and nutrients to new tissue masses. The tyrosine kinase inhibitor **semaxanib** (**29-4**) has shown promising early activity against solid tumors; this compound inhibits neoangiogenisis and also shows anti-metastatic activity. Villsmeyer-type reaction of 3,5-dimethylpyrrole (**29-1**) affords the corresponding carboxaldehyde (**29-2**). Condensation of this intermediate with indolone itself (**29-3**) in the presence of a base affords semaxanib (**29-4**) [30].
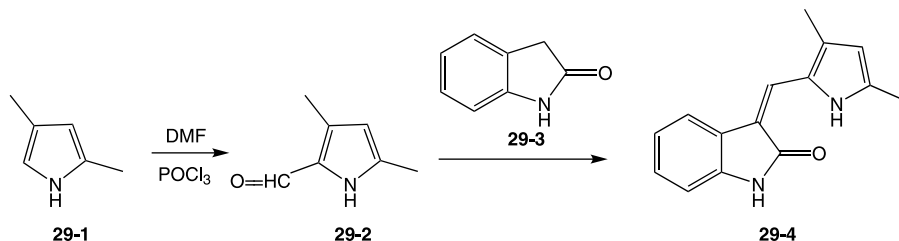
   The synthesis of a structurally somewhat more complex indolone tyrosine kinase inhibitor starts with the construction of the pyrrole ring. Reaction of *tert*-butyl aceto-acetate (**30-1**) with nitrous acid leads to nitrosation on the activated methylene carbon (**30-2**). This introduces the nitrogen atom that will appear in the target pyrrole. Condensation of that product with ethyl acetoacetate (**30-3**) completes the formation of the pyrrole ring (**30-4**). The strategy depends on the presence of the carboxyl groups at the 2 and 4 positions, which have esters with differing reactivities. Thus, treatment of the diester (**30-4**) with aqueous acid leads to hydrolysis of the carboxyl adjacent to the ring nitrogen; that then decarboxylates under reaction conditions (**30-5**). Reaction of this intermediate with methyl orthoformate in a strong acid then introduces a formyl group at the only open position on the ring (**30-6**). Condensation of this aldehyde with indolone (**29-3**), as above, leads to the formation of the analogue of (**29-4**) that carries in addition a carboxyl group on the pyrrole ring (**30-7**). Saponfication then affords the free acid (**30-8**). Reaction of this compound with *N,N*-diethyl ethylenediamine gives the corresponding amide. There is thus obtained the tyrosine kinase inhibitor **sunitinib** (**30-9**) [31].
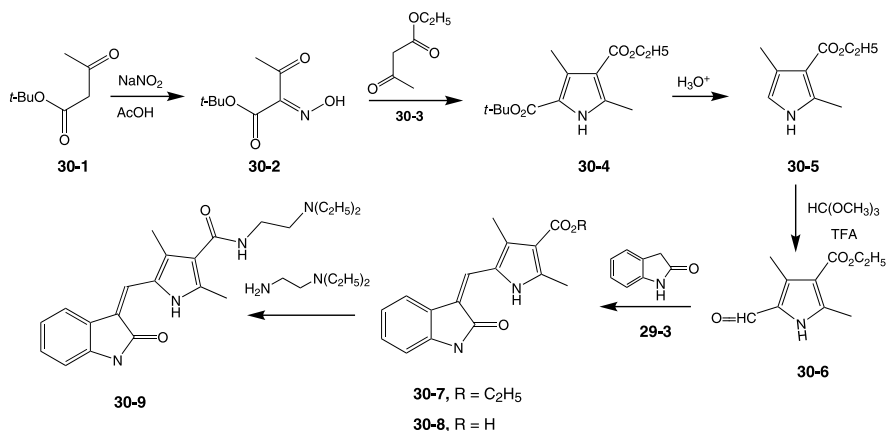
   The association between Alzheimer's disease and levels of acetycholine has led to renewed interest in cholinergic agents. Though the substituted indolone **linpirdine** (**31-8**) was found to stimulate the release of acetylcholine in some animal models, the compound failed as a treatment for Alzheimer's. The synthesis starts with a standard scheme for preparing indoxyls. Thus, acylation of diphenylamine (**31-1**) with oxalyl chloride leads to the amide (**31-2**). The acid chloride then cyclizes into the ring on heating to afford (**31-3**). Reaction of that product with 4-picoline (**31-4**) under phase transfer conditions catalyzed by a quaternary salt affords the carbinol (**31-5**) from addition of the transient anion on the methyl group of the picoline to the more electrophilic carbonyl group. The alcohol is then dehydrated by means of acetic anhydride and the resulting olefin hydrogenated to afford the indolone (**31-6**). The 3 position of the indolone is now activated by the adjacent benzene ring on one side and the carbonyl group on the other. Alkylation with α-chloropicoline (**31-7**) proceeds with hydroxide as the base to afford linpiride (**31-8**) [32].
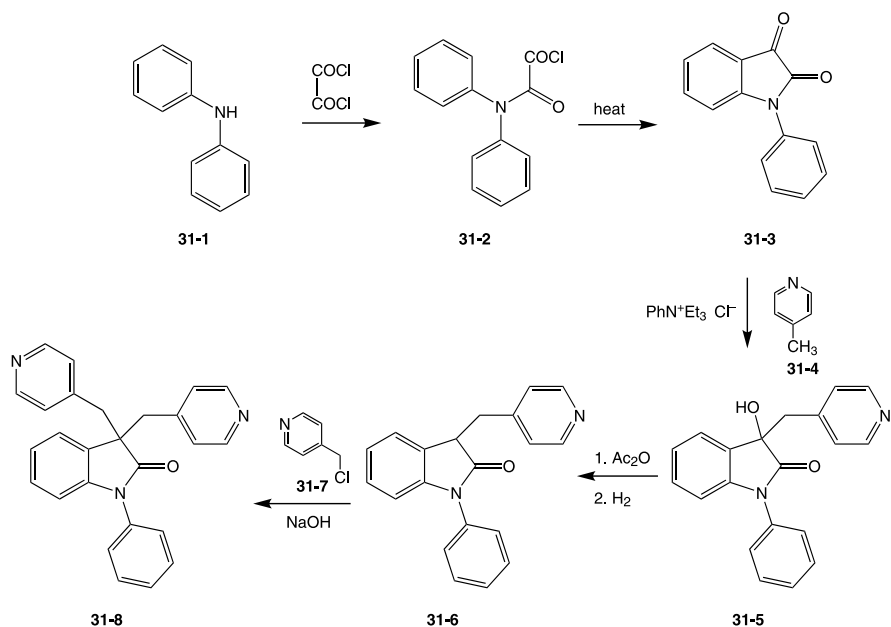
An indolone comprises a prominent moiety in the dopamine D2 selective anti-psychotic agent **ziprasidone** (**32-8**). Reduction of the ketonoid carbonyl group on the indoxyl (**32-1**) under Wolff–Kischner conditions affords the indolone (**32-2**). Acylation of the product with chloroacetyl chloride in the presence of aluminum chloride then affords the reactive chloroacetyl derivative (**32-3**). In a convergent sequence, reaction of isothiazolone (**32-4**) with phosphorus oxychloride leads to
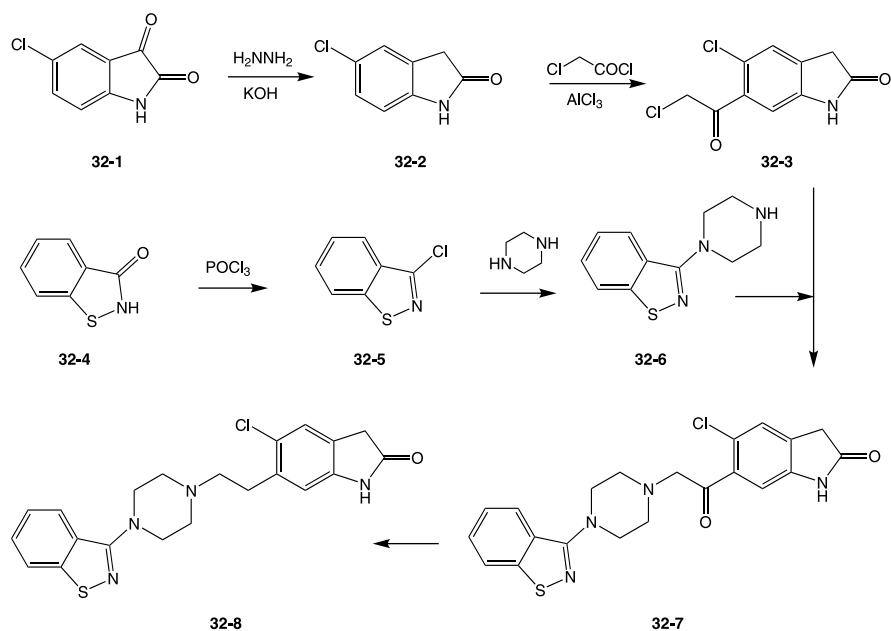
the enol chloride (**32-5**). Reaction of that intermediate with piperazine yields the alkylation product (**32-6**). Reaction of this with the chloroketone (**32-3**) results in alkylation on the second piperazine nitrogen and the formation of (**32-7**). Reduction of the aryl-carbonyl function completes the synthesis of ziprasidone (**32-8**) [33].

The isoindolone ring system forms the nucleus for one of the more traditional "profen" NSAIDs. Reduction of the nitro group in arylpropionic acid (**33-1**) gives the corresponding aniline (**33-2**). Reaction of that intermediate with the imide (**33-3**) from phthalic anhydride gives the product (**33-4**) in which the aniline nitrogen has exchanged with ammonia. Treatment of the new imide with zinc in acetic acid leads, interestingly, to reduction of but one of the carbonyl groups to afford the indolone (**33-5**), **indoprofen** [34].
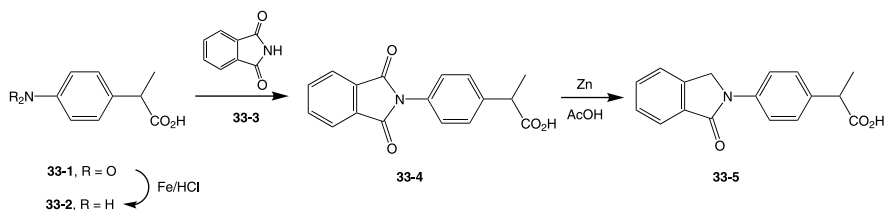
Imide exchange provides the starting material for a sulfonamide diuretic agent whose structure incorporates many of the features of the agents noted in Chapter 2. Reaction of the phthalimide (**34-1**) with cyclohexylamine (**34-2**) provides the intermediate (**34-3**). Treatment of that intermediate with tin in the presence of acid reduces one of the carbonyl groups (**34-4**). Nitration proceeds as would be predicted at the position *meta* to the carbonyl group (**34-5**); this is then reduced to the aniline (**34-6**) by means of stannic chloride. The amino group is then converted to the diazonium salt with nitrous acid; Sandmeyer reaction with sulfur dioxide in the presence of cuprous chloride affords the corresponding sulfonyl chloride (**34-7**). That is then treated with ammonia to give the diuretic **clorexolone** (**34-8**) [35].
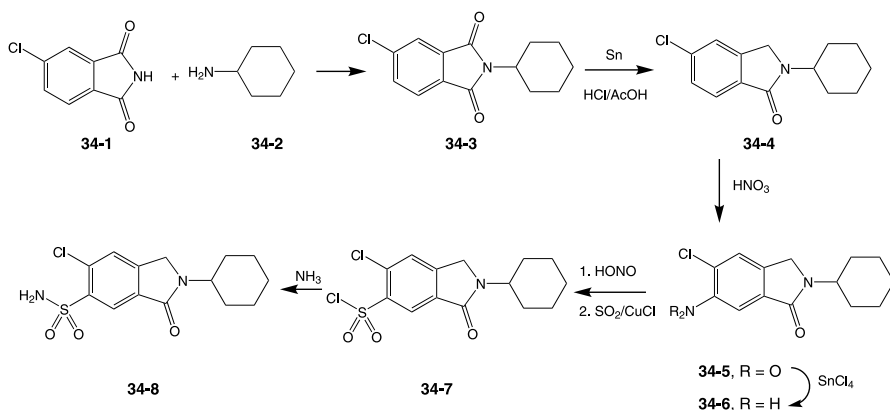
The low level of research that continued on thalidomide, in spite of its ill repute, unexpectedly showed that the compound affected immune function. The drug was, for example, recently approved by the FDA for treatment of complications from leprosy; it has also been investigated as an adjunct for treating some malignancies.
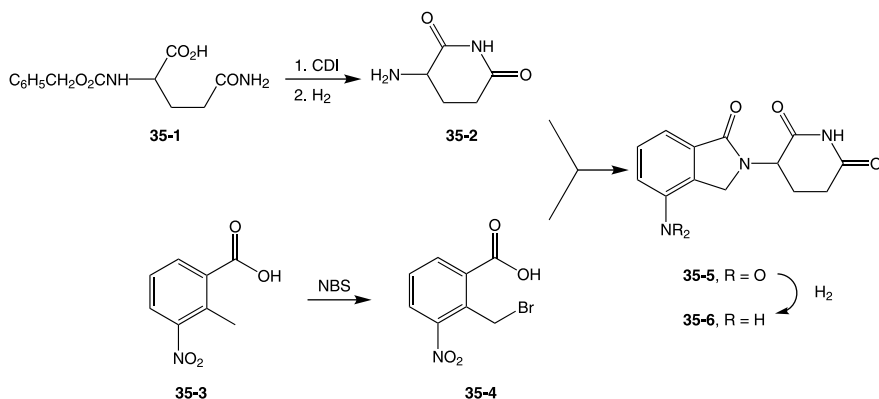
Recent research on related compounds has revealed a series that inhibits tumor necrosis factor (TNF-α). Synthesis of the aminosuccinimide moiety starts by cyclization of carbobenzyloxy glutamine (**35-1**) by treatment with carbonyl diimidazole. Catalytic hydrogenation of the first-formed product removes the protecting group (**35-2**). The aromatic moiety of the target compound is prepared by free radical bromination of the methyl group in the benzoic acid (**35-3**) to give the bromomethyl derivative (**35-4**). Condensation of this last with the succinimide (**35-2**) leads to isoindolone (**35-5**). A second hydrogenation step reduces the nitro group to an aniline to afford **lenalidomide** (**35-6**) [36].

A related sulfonamide is classed as an isoindolone by virtue of typical benzoyl-benzoic acid "pseudoacid" isomerism. The amino group in benzoylbenzoic acid
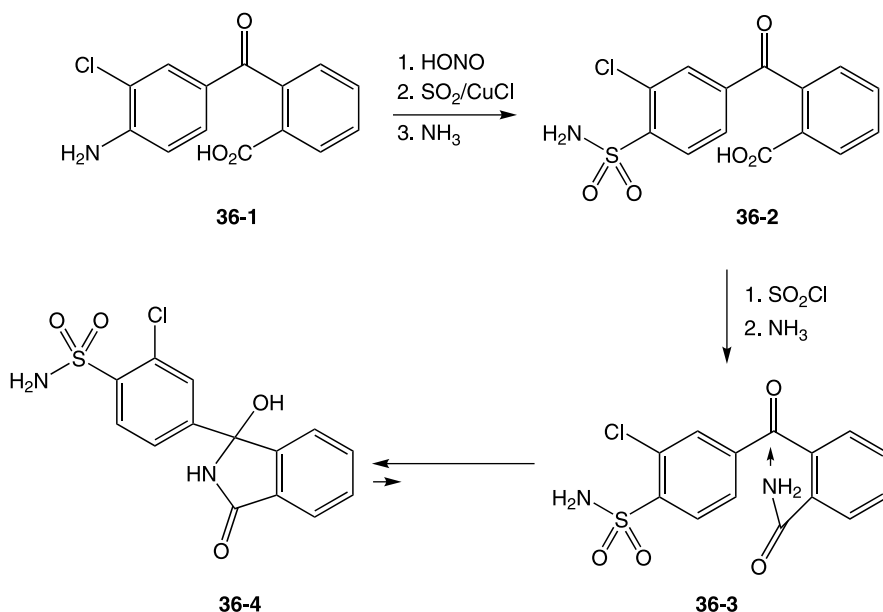
(**36-1**) is converted to a sulfonamide by an essentially the same sequence as that used above to give (**36-2**). The carboxylic acid is then converted to the amide (**36-3**) by sequential conversion to the acid chloride and reaction with ammonia. The amide nitrogen then adds to the benzoyl group to give isoindolone (**36-4**) in a reaction typical of *ortho* benzoyl benzoates [37]. This closed form of the widely used diuretic agent **chlorthalidone** (**36-3**) greatly predominates over the open isomer with which it can equilibrate.

10.2. COMPOUNDS THAT CONTAIN TWO HETEROATOMS

10.2.1. Indazoles

The readily prepared indazole ring system has found surprisingly little use as a nucleus for therapeutic agents. The preparation for the common intermediate (**37-4**) for two of these agents starts with the reaction of the *N*-benzyl derivative (**37-1**) from methyl anthranilate with nitrous acid to give the *N*-nitroso derivative (**37-2**). Reduction by means of sodium thiosulfate leads to the transient hydrazine (**37-3**), which undergoes spontaneous internal hydrazide formation to form (**37-4**). The enolate from reaction of this amide with sodium methoxide gives the product from alkylation on oxygen. Thus, treatment of the enolate with 3-chloro-1-diethylamino-propane gives **benzydamine** (**37-5**) [38], a compound that has been extensively investigated for its unusual anti-inflamatory activity. Alkylation of that same anion with methyl chloroacetate affords the corresponding ester. This gives the more classical NSAID **bendazac** (**37-6**) after hydrolysis of the ester grouping [39].
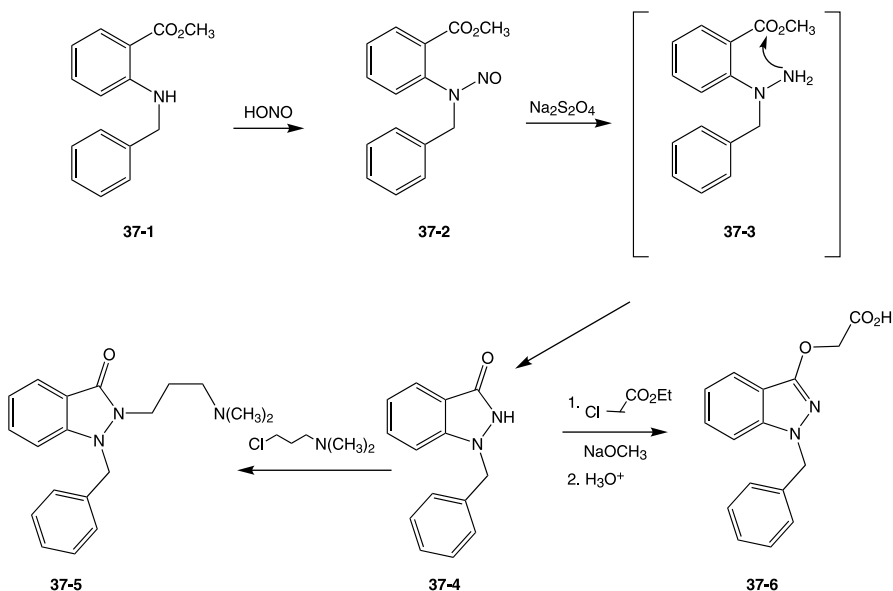
Interposing an additional carbon atom between the indazole nucleus and the acetic acid side chain provides another compound that shows anti-inflammatory activity in model systems. Reduction of the carboxylic acid in the indazole (**38-1**) by means of lithium aluminum hydride leads to the carbinol (**38-2**). Alkylation of the enolate from the alcohol with methyl 2-bromo-2-methylpropionate leads to the corresponding ether. Saponification gives the free acid and thus **bindarit** (**38-3**) [40].
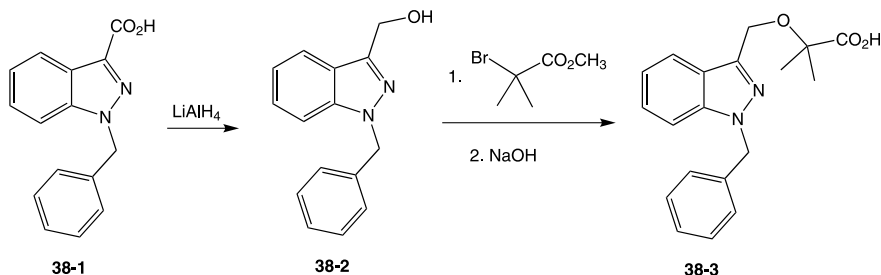
Partial reduction of the aromatic ring leads to a compound that acts as an analgesic anti-inflamatory agent, though the structure lacks any of the features typically found in NSAIDs. The starting thioamido ketone (**39-1**) is available from acylation of cyclohexanone with methyl isothiocyanate. Reaction of that compound, shown as its enol tautomer, with methylhydrazine can be envisaged to involve the initial formation of the addition–elimination product (**39-2**). Additition of the more basic nitrogen to the thiocarbonyl function then leads to the formation of a pyrrazole ring. There is thus obtained **tetrydamine** (**39-3**) [41].
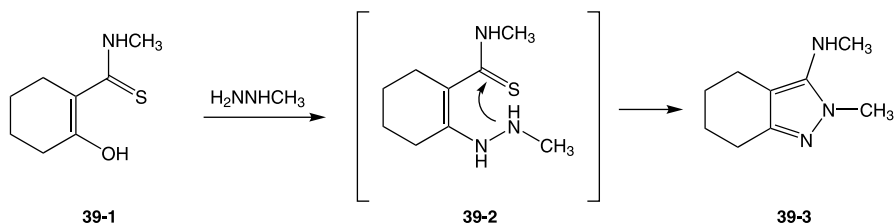
10.2.2. Benzimidazoles

A sizeable, if largely disparate, group of therapeutic agents are based on the benzimidazole nucleus; this heterocyclic system does, however, provide a unifying theme for the subset of anthelmintic compounds that include this moiety, discussed at the end of this section.

Benzimidazoles substituted with an alkylamine at position 2 have a venerable history as H_1 antihistaminic agents. The standard starting material for many benzimidazoles consists of phenylenediamine (**40-1**), or its derivatives. Reaction of that compound with chloroacetic acid can be rationalized by invoking initial formation of the chloromethyl amide (**40-2**). Imide formation with the remaining free amino group closes the ring to afford the 2-chloromethyl benzimidazole (**40-3**). Displacement of

halogen with pyrrolidine affords the alkylation product (**40-4**). The proton on the fused imidazole nitrogen is then removed by reaction with sodium hydride. Treatment of the resulting anion with α,4-dichlorotoluene gives the H_1 antihistaminic agent **clemizole** (**40-5**) [42].
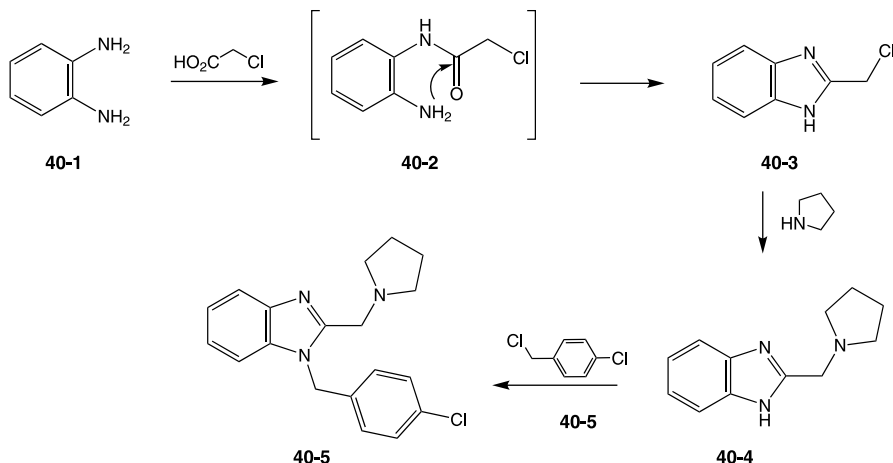
Considerable work has been devoted to the search for agents devoid of the sedative effect that accompanied some of the earlier antihistamines. One stratagem for achieving that comprises adding a function that will diminish the likelihood that the drug will cross the blood–brain barrier. The antistamine **emedastine** (**41-3**), for example, incorporates a terminal ether that can be potentially metabolized to a carboxylic acid. Alkylation of the imidazole (**41-1**), available from imidazol-2-one by reaction with phosphorus oxychloride, with the chloroether (**41-2**) leads to a reaction on nitrogen to afford (**41-3**). Displacement of the enol chloride in that intermediate with *N*-methyl-1-4-diazepine (**41-4**) leads to emedastine (**41-5**) [43].
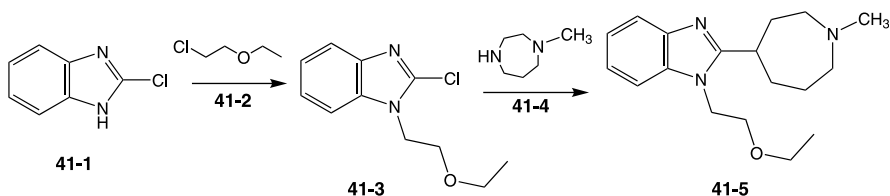
The widely used drug **astemizole** (**42-7**) is also nonsedating and presumably does not cross the blood–brain barrier. The structure of the compound does not, however, present any obvious polar groups. The preparation of this structurally complex compound starts by addition of phenylenediamine (**40-1**) to the protected isothiocyanate (**42-1**) to afford thiourea (**42-2**). The requisite imidazole ring is then formed by treatment with a base, a reaction that probably involves addition–elimination of the amine to the thiourea function in the enol form (**42-3**). The imidazole ring nitrogen is then converted to its anion; alkylation with 4-fluorobenzyl bromide (**42-4**) then gives the intermediate (**42-5**). The protecting group on piperidine nitrogen is then removed by

sequential saponification of the urethane followed by acidification with consequent decarboxylation of the amine carbonate. Alkylation of the newly revealed basic nitrogen with 4-methoxyphenethyl bromide (**42-6**) leads to **astemizole** (**42-7**) [44].
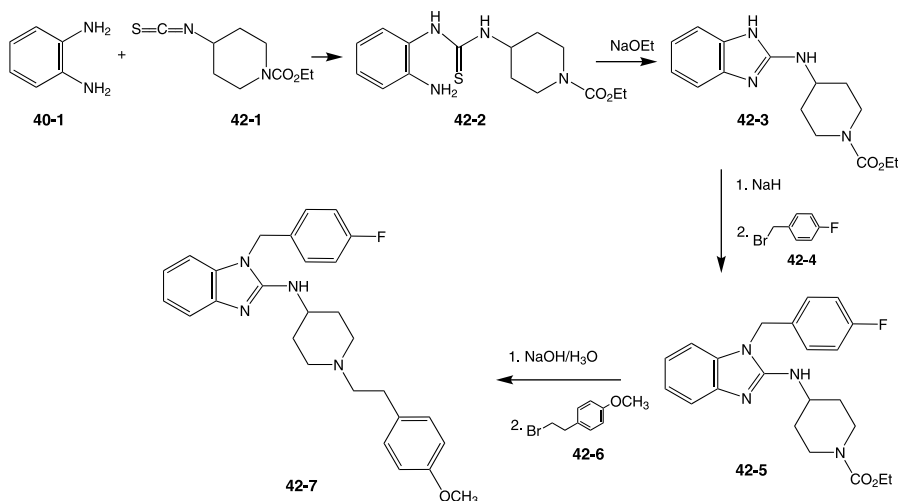
Aromatic nucleophilic displacement of the highly activated chlorine in 2,4-dinitrochlorobenzene, (**43-1**) by means of *N,N*-diethylethylenediamine (**43-2**) gives the corresponding aniline (**43-3**). Reaction of that compound with ammonium sulfide interestingly leads to the selective reduction of the nitro group adjacent to the newly introduced amino group to afford the *ortho* diamine (**43-4**); the selectivity may be due to the localization of the reducing function by the initial sulfide salt formation with the *ortho* amino group. Condensation of the diamine (**43-4**) with the iminoether (**43-5**) from 4-ethoxyphenylacetonitrile leads to benzimidazole ring formation [45]. The product, **etonitazine** (**43-6**), is a potent opioid analgesic. The structure of this
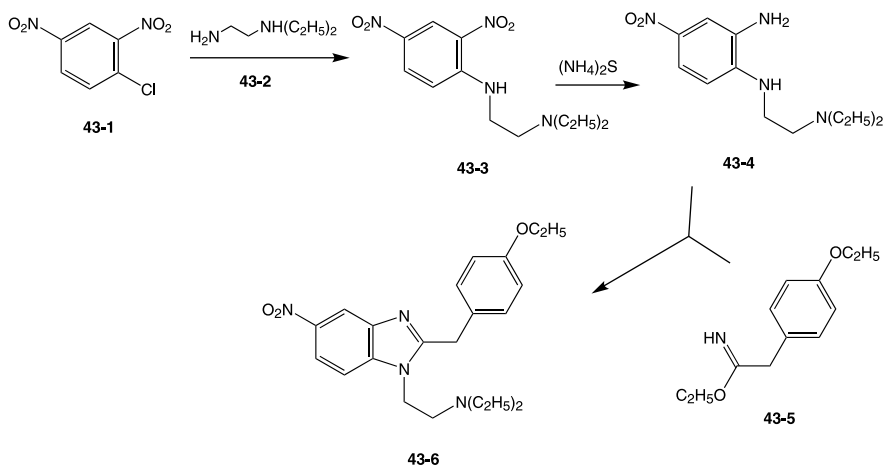
compound at first sight differs markedly from the opioids discussed in Chapter 7; it will, however, provide a good fit when overlaid with those, though this requires some departures from energy minimized conformations.

The majority of clinically effective antiviral agents consist of subtly modified nucleosides. The side effects of many of these drugs, thought to be due to the very intimate involvement of nucleosides in many biological regulatory processes, has led to a continuing search for nonnucleoside antiviral compounds. One of these, **enviroxime** (**44-5**), is based on a benzimidazole nucleus. Reaction of benzoylphenylenediamine (**44-1**) with cyanogen bromide probably proceeds initially to give the *N*-cyano intermediate (**44-2**). Attack on the nitrile group by the adjacent amine closes the ring with the consequent formation of the 2-aminobenzimidazole (**44-4**). Treatment of that product with sodium hydride leads to the selective formation of the anion on the ring nitrogen *meta* to the carbonyl group; one might have predicted the ionization of the other, less electron-dense ring position. Addition of *is*-propylsulfonyl chloride leads to the formation of the sulfonamide (**44-4**). The ketone is then converted to its oxime by reaction with hydroxylamine hydrochloride and sodium acetate. The predominant product is the slightly less sterically encumbered E isomer **enviroxime** (**44-5**) [46]. Antiviral activity is retained when the oxime is replaced by the sterically similar ethylidene group. This compound is obtained by first condensing the ketone (**44-4**) with an organometallic such as ethylmagnesium bromide, followed by dehydration of the resulting alcohol with acetic acid. This affords predominantly the E-isomer **enviradene** (**44-6**) [47].
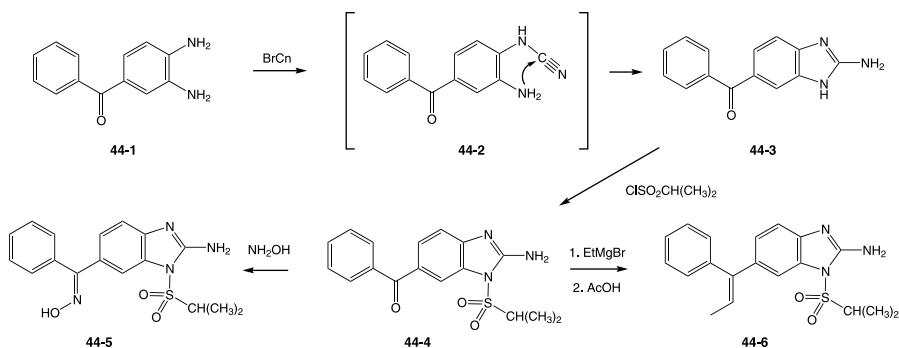
Purines in which the sugar moiety is replaced by an abbreviated open chain surrogate, for example acyclovir, comprise an important group of antiviral drugs. In a somewhat similar vein, the purine may be replaced by benzene, though the example at hand includes a normal sugar. Thus, coupling of the benzimidazole (**45-1**) with the tetracetyl ribofuranoside (**45-2**) in the presence of *N,O*-bistrimethylsylil acetamide affords the glycosilated benzimidazole (**45-3**). Treatment on this intermediate with isopropylamine leads to the displacement of the bromine on the imidazole ring by isopropyl amine (**45-4**). Saponification with aqueous sodium carbonate removes the acetyl protecting groups to afford the antiviral agent **maribavir** (**45-5**) [48].
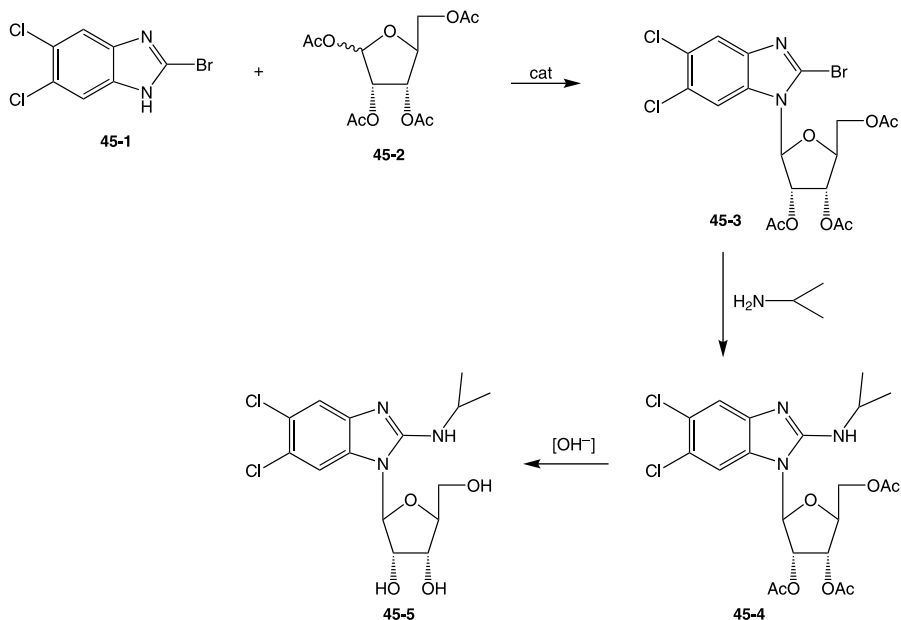
Condensation of 2,3-diaminobenzophenone (**44-1**) with acetamidine affords the corresponding 2-methylbenzimidazole (**46-1**). Reduction of the carbonyl group leads to the benzhydryl alcohol (**46-2**). The benzhydryl hydroxyl readily undergoes replacement, by nitrogen on imidazole, speculatively via a loss of hydroxyl to form a transient carbocation that then picks up the basic nitogen. The product, **irtemazole** (**46-3**) [49], has proven useful in treating gout by promoting the excretion of uric acid.
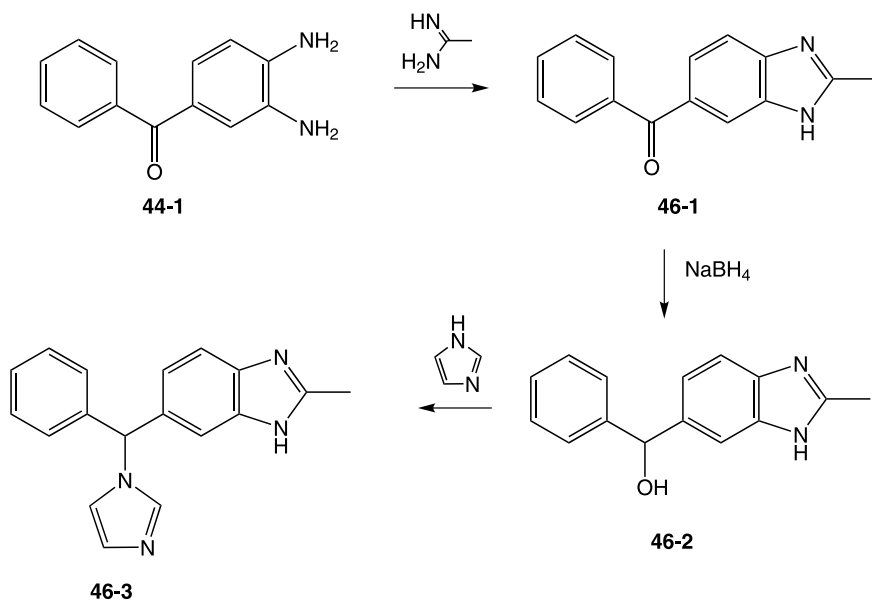
The anti-ulcer histamine H$_2$ antagonists, discussed in Chapter 8, which act by blocking histamine-stimulated gastric acid secretion, have proven so effective and safe that they are now approved in the United States at least for nonprescription. The benzimidazoles discussed below, which achieve the same overall therapeutic effect, act more directly on stomach acid by inhibiting the sodium-potassium pump enzyme responsible for acid secretion. Reaction of methoxylated phenylenediamine (**47-1**) with potassium ethylxanthate, from sodium ethoxide and carbon disulfide, gives the benzimidazole-2-thiol (**47-2**). In the convergent scheme, the hydroxy-methylpyridine (**47-3**) is converted to the corresponding chloride (**47-4**). Reaction of that intermediate with thiol (**47-2**) in the presence of a base leads to the formation of the thioether. Controlled oxidation of sulfur with a single equivalent of peracid leads to the sulfoxide, **omeprazole** (**47-5**) [50]. This drug, too, is now available over-the-counter; prescriptions are still needed, however, for esomeprazole, the pure enantiomer responsible for the activity.
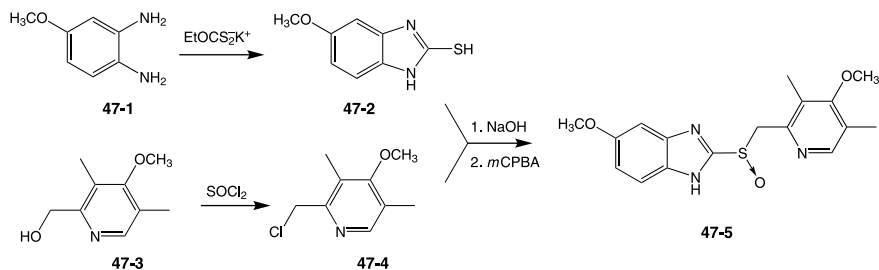
An analogue of that compound shifts one of the methoxyl groups from the benzi-midazole to the pyridine ring. Preparation of the requisite intermediate illustrates some typical pyridine chemistry. Thus, aromatic nitration of the pyridine N-oxide (**48-1**) leads to the 4-nitro intermediate (**48-2**). The presence of the N-oxide at the 4 position activates the nitro group toward nucleophilic displacement, which is achieved by reaction with sodium methoxide, which leads to the introduction of a second methoxy group (**48-3**). Heating that product with acetic anhydride leads to Polonovski rearrangement and a formal shift of oxygen from the ring nitrogen to
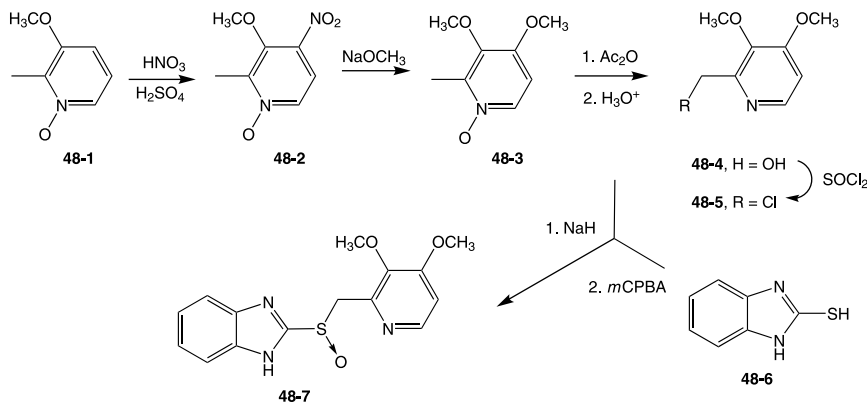
the methylene group at the 2 position. Saponification of the product leads to the key intermediate (**48-4**). This is then converted to the chloride (**48-5**). Reaction of that with benzimidazole-2-thiol (**48-6**) followed by oxidation of the resulting thioether affords the anti-ulcer agent **pantoprazole** (**48-7**) [51].

In much the same vein, nitration of 2,3-dimethylpyridine *N*-oxide (**49-1**) affords the nitro derivative (**49-2**). The newly introduced nitro group is then displaced by the alkoxide from 3-methoxypropanol to afford the corresponding ether (**49-3**). Proceeding much as above, the methyl group at the position adjacent to the nitrogen is converted to its chloride (**49-5**). Condensation with benzimidazol-2-thiol then affords **rabeprazole** (**49-6**) [52].
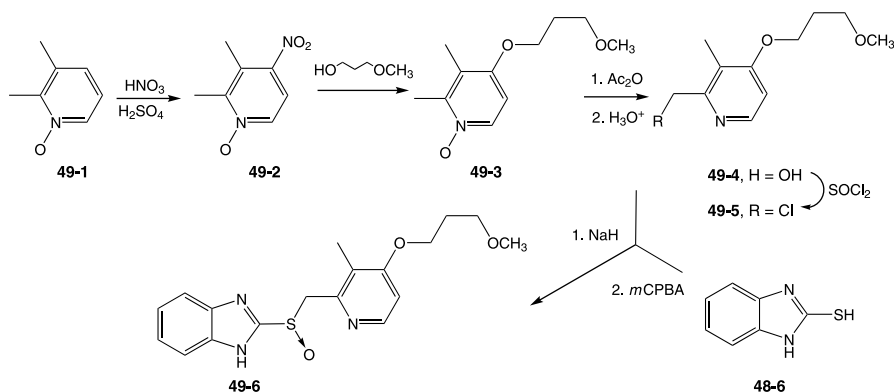
Helminths comprise a very large class of worm-like organisms, many of which parasitize humans. These include the nematodes that are responsible for debilitating gastrointestinal infections. The benzimidazoles provided the first truly broad-spectrum antinematodal agents. The efficacy of this class of drugs combined with the development of drug-resistant strains led to the development of scores of analogues. The few anthelmintic benzimidazoles discussed below thus do not truly reflect the size of the research effort and have been selected on the basis of chemistry. Chemical considerations, it should be noted, also caused a distortion of chronology since the first drug to be introduced (in 1961) was in fact **thiabendazole** (**53-6**). An appropriately substituted *ortho*-phenylenediamine constitutes the key intermediate to the preparation of all but that last benzimidazole.

Alkylation of the phenolic group in aminophenol (**50-1**) with propyl bromide in the presence of potassium hydroxide gives the ether (**50-2**). Nitration with the usual mixture of nitric and sulfuric acids proceeds at the position *ortho* to the amido group; saponification followed by reduction of the nitro group then gives the desired diamine (**50-5**). Reaction of that intermediate with the S-methyl ether of thiourea can be visualized as proceeding first to the guanidine (**50-6**) obtained by addition to the imine double bond followed by elimination of methyl mercaptan. Cyclization completes the construction of the 2-aminobenzimidazole compound (**50-7**). Acylation with methyl chloroformate results in the formation of a urethane on the amino group, in contrast to alkylation (**42-3** → **42-5**), which proceeds on ring nitrogen. There is thus obtained **oxbendazole** (**50-8**) [53].
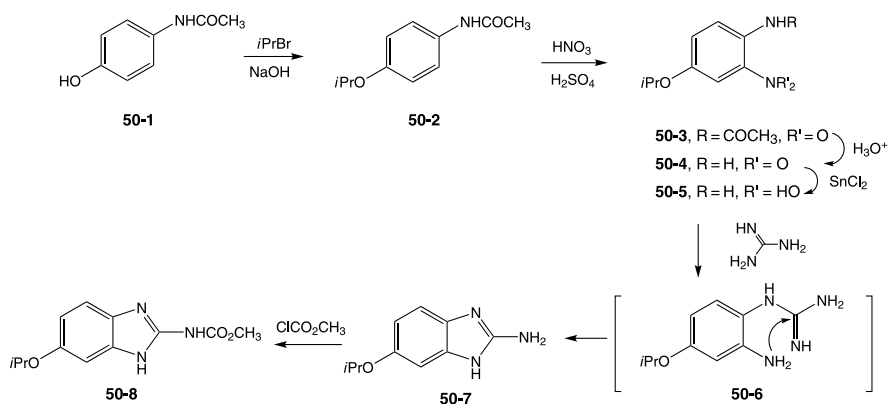
Nucleophilic aromatic substitution provides the key reaction to building the phenylenediamine in a somewhat more complex aminobenzimidazole. The starting material (**51-2**) is obtained by nitration of the fluorothiophenone (**51-1**). Reaction of that product, in which the good leaving group, fluorine, is activated by electron withdrawing groups at both the 2 and 4 positions, with amide anion affords the aniline (**51-3**). The nitro group is then reduced by catalytic hydrogenation to give diamine (**51-4**). Reaction of that intermediate with the *S*-methylthiourea (**51-5**), which already includes the requisite methylurethane function, leads directly to the antinematodal benzimidazole, **nocodazole** (**51-6**) [54].
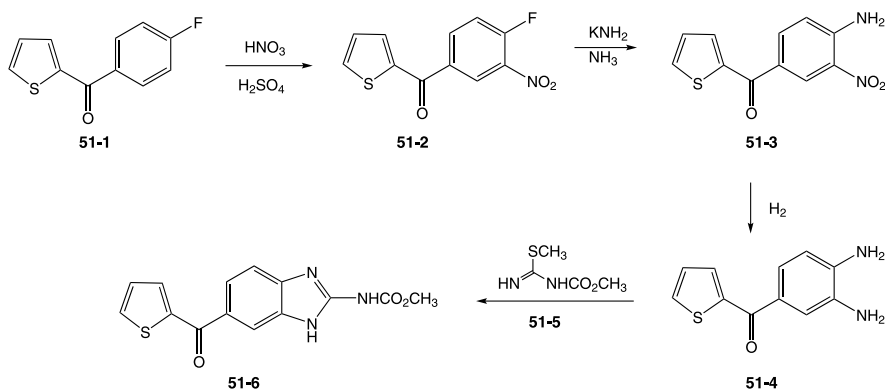
Nucleophilic aromatic displacement is invoked for incorporation of the side chain in yet another benzimidazole. Thus, treatment of 2,5-dinitroacetanilide (**52-1**) with the anion from mercaptomethylcyclohexane leads to the unusual displacement of one of the nitro groups and the formation of thioether (**52-3**). This intermediate is then converted to diamine (**52-4**) by sequential reduction and hydrolysis of the amide. Condensation with the same thiourea derivative as above affords **dribendazole** (**52-5**) [55].
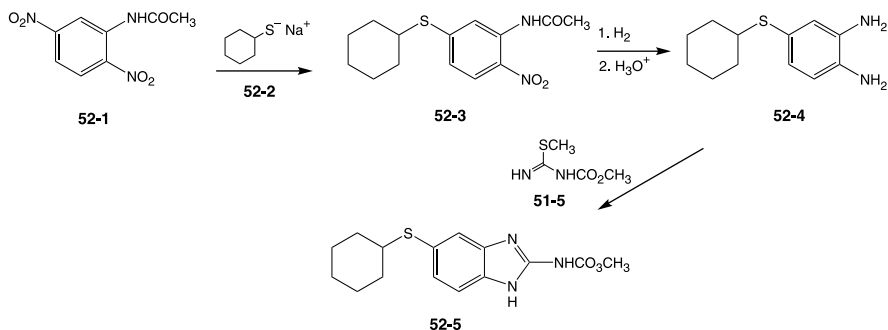
Preparation of the prototype drug departs from the phenylenediamine strategy used in all of the previous examples. Condensation of thiazolo nitrile (**53-2**) with aniline catalyzed by aluminum chloride affords the amidine addition product (**53-3**). This is then converted to its reactive *N*-chloro derivative (**53-4**) by reaction with sodium hypochlorite. Treatment of that intermediate with a base such as potassium hydroxide leads directly to the cyclization product and thus the benzimidazole **thiabendazole** (**53-6**) [56]. The reaction can be rationalized by invoking as the first step the abstraction of chloride to leave behind a nitrene species such as (**53-5**); this would then readily insert in the CH bond at the *ortho* position.
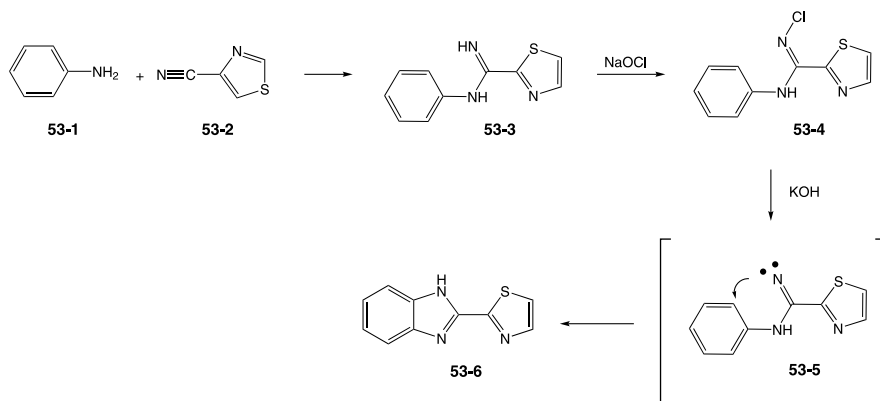
Further substitution on this compound leads to a somewhat more potent antinematodal drug. Nitration of (**53-6**) under the usual conditions leads to the corresponding nitro derivative (**54-1**). The nitro group is then reduced to the corresponding amine (**54-2**). Acylation with isopropyl chloroformate forms the corresponding carbamate and thus **cambendazole** (**54-3**) [57].
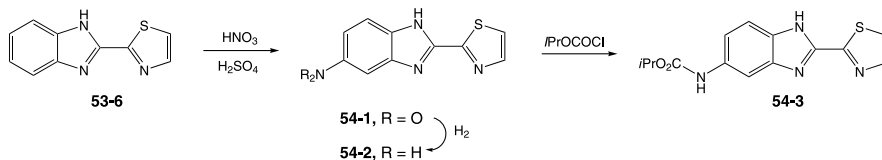
A benzimidazole can serve as the terminal nitrogen-containing moiety in an angiotensin receptor antagonist. Esterification of 3-nitrophthalic acid (**55-1**) takes place at the less hindered of the two carboxyl groups to afford the half-ester (**55-2**). The free acid is then converted to its azide by way of the acid chloride. Heating that compound in *tert*-butanol leads to Curtius rearrangement to form the corresponding isocyanate; this reacts with solvent to afford the urethane (**55-3**). Alkylation of that function with the biphenyl derivative (**55-4**) (see Chapter 8) leads to an intermediate (**55-5**) that now incorporates the requisite chain. The nitro group is then reduced by catalytic hydrogenation to the amine (**55-6**). Sodium ethoxide cleaves the urethane and at the same time replaces the methyl ester with its ethyl counterpart. Reaction of the resulting diamine with ethyl orthoformate leads to the formation of the benzimidazole ring (**55-7**). Conversion of the nitrile to a tetrazole by means of sodium azide in acid followed by saponification of the ester affords the antagonist **candesartan** (**55-8**) [58].
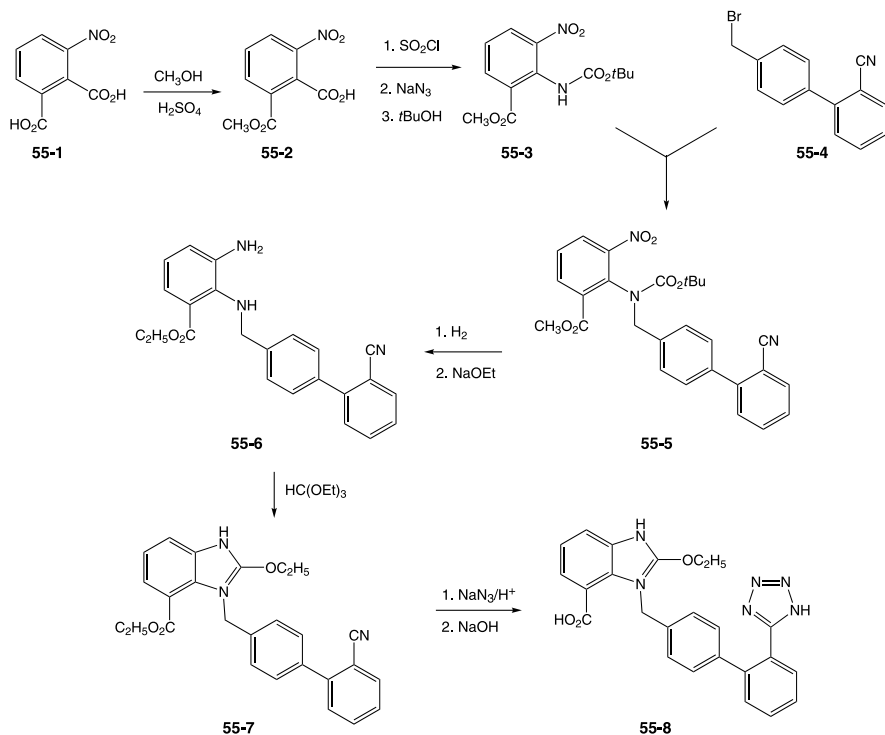
Inhibitors of the blood clotting factor thrombin would in principle prove useful in preventing inappropriate clot formation that potentially leads to stroke and heart attack. Reaction of the carboxylic acid (**56-2**) with thionyl chloride leads to the corresponding acid chloride (**56-3**). Treatment of that intermediate with the substituted pyridyl amine (**56-1**) leads to the amide (**56-4**). Catalytic hydrogenation of (**56-4**) reduces the nitro group to the primary amine (**56-5**). Condensation of that *ortho*-diamine with the carboxylic acid (**56-6**) in the presence of carbonyl diimidazole

connects those two moieties while forming the imidazole ring (**56-7**). This reaction proceeds via the amide formed with the primary amine followed by replacement of the amide carbonyl oxygen by the adjacent amine. Reaction of this last intermediate with ammonium carbonate leads to addition of ammonia to the nitrile to form an amidine. Saponification of the side chain ester affords the thrombin inhibitor **dabigartan** (**56-8**) [59].
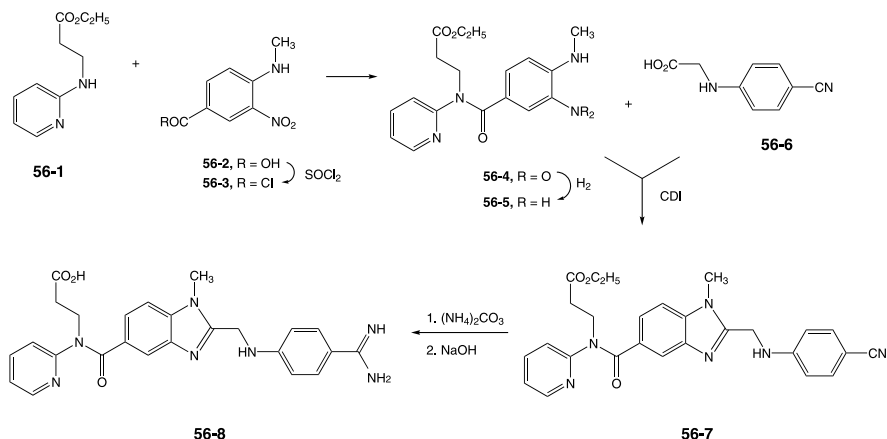
Nausea that accompanies the administration of cancer chemotherapy agents was resistant to drug intervention until the introduction of the serotonin receptor antagonist **odansetron** (see Chapter 13). The benzimidazolone-based compound **itasetron** (**57-6**) has much the same activity as its tricylcic predecessor. Condensation of 2-nitrophenyl-isocyanate (**57-1**) with the bridged bycyclic diamine (**57-2**) leads to the addition
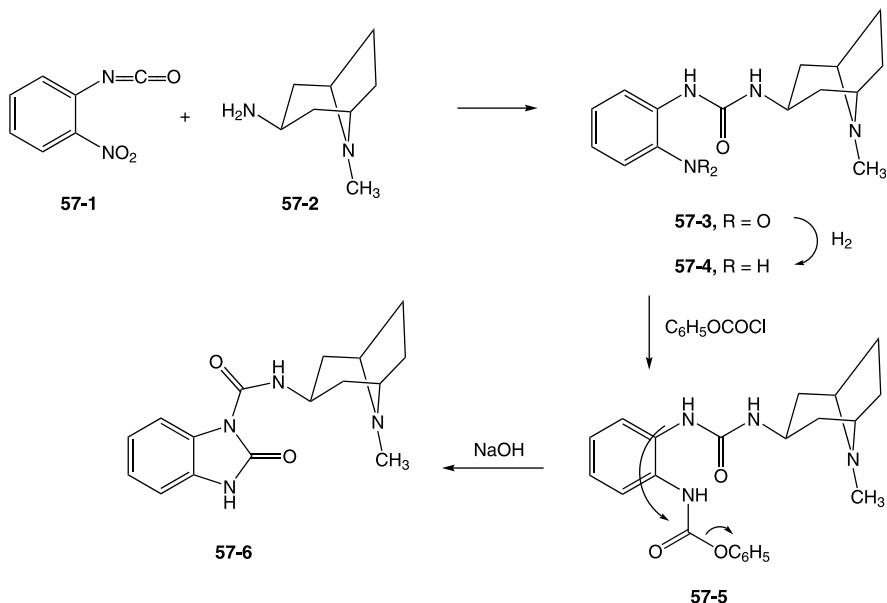
product, urea (**57-3**). The nitro group is next reduced by catalytic hydrogenation to afford the corresponding aniline (**57-4**). Acylation of the newly formed amine with phenyl chloroformate leads to the urethane (**57-5**). Treatment of that product with a base leads to the formation of the benzimidazolone ring (**57-6**). The transform can be rationalized by assuming that the anion from abstraction of a proton from urea nitrogen attacks the urethane carbonyl group. Expulsion of phenoxide will then close the ring to afford itasetron (**57-6**) [60].

10.2.3. Benzoxazoles and Benzisoxazoles

A reasonable number of leukotriene receptor antagonists are now available for treating leukotriene-provoked asthama. The antiasthmatic agent **ontazolast** (**58-7**), on the other hand, approaches that disease by inhibiting the synthesis of leukotrienes. Condensation of pyridine 2-aldehyde (**58-1**) with the Grignard reagent from bromomethylenecyclohexane affords the corresponding carbinol. Oxidation of that benzylic-like alcohol with manganese dioxide affords the ketone (**58-2**). Reductive amination by means of ammonium formate in the presence of formic acid leads to replacement of the carbonyl group by a primary amine (**58-3**). In a convergent scheme, reaction of aminotoluol (**58-4**) with carbon disulfide in the presence of a base proceeds to the addition product, benzoxazole (**58-5**). The thiol at the 2 position is then replaced by halogen by reaction with phosphorus oxychloride (**58-6**). Displacement of the chlorine in that product by the primary amine in the other half of the molecule leads to the alkyalation product (**58-7**) and thus **ontazolast** [61].
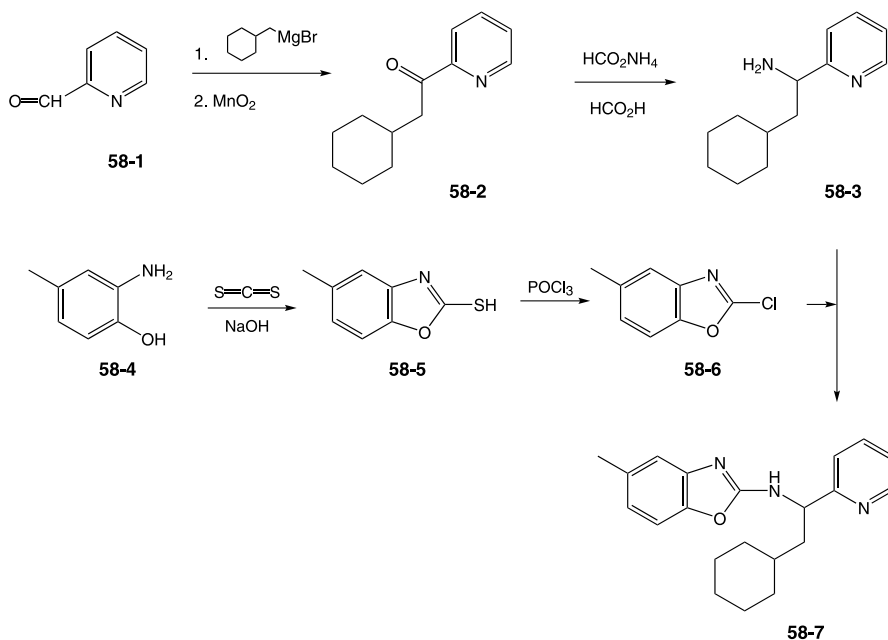
Many new antipsychotic compounds that have been introduced over the years have shown decreased side effects in initial trials. The promise of such "atypical" agents often did not stand up with chronic use. Yet another atypical drug is a mixed agonist/antagonist at dopamine receptors. The partial agonist activity should in theory avoid the effects of excessive blockade. The compound at hand also acts on 5HT receptors; this should help patients who suffer from bipolar disorders in the depressed phase of the disease. Alkylation of the nitrogen on the piperazine (**59-1**) with the 3-bromobenzyl mesylate (**59-2**), obtained by reaction of the corresponding alcohol with methanesulfonyl chloride, affords the intermediate (**59-3**). The additional benzene ring is added by Suzuki cross-coupling with phenylboronic acid. There is thus obtained the antipsychotic compound **bifeprunox** (**59-4**) [62].
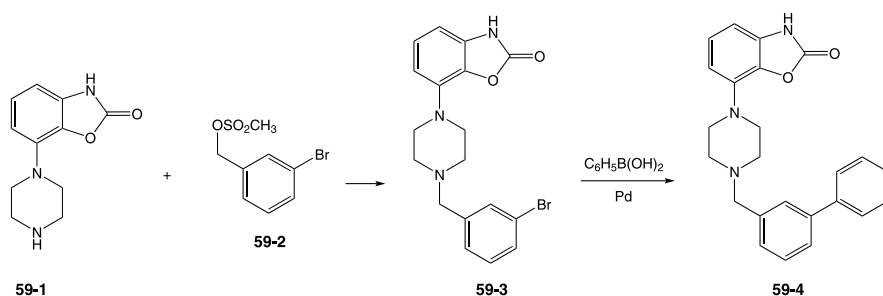
The association between acetylcholine levels and Alzheimer's disease, as noted more than once previously, has led to the search for novel compounds that raise the level of that neurotransmitter by inhibiting acetylcholinesterase, the agent of its inactivation. The benzisoxazole **icopezil** (**60-8**) has undergone several trials against that debilitating disease as a result of selective cholinesterase inhibiting activity in the CNS. Friedel–Crafts acylation of the indolone (**60-1**) with acetyl chloride affords the methyl ketone (**60-2**). This is then converted to its oxime and that function acylated with acetic anhydride to yield (**60-3**). Treatment with pyridinium perbromide
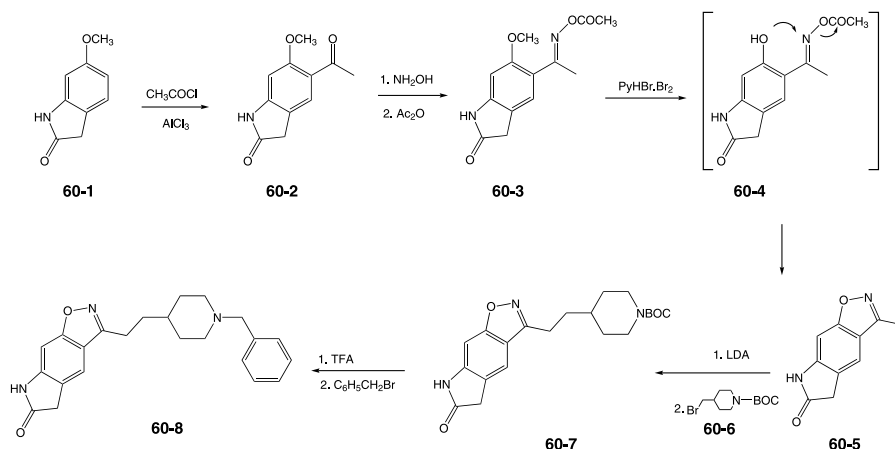
then cleaves the methyl ether on the ring, forming the transient intermediate (**60-4**). Phenol-oxygen then displaces the acetyl group on the oxime, leading to the benzisoxazole nucleus (**60-5**). The carbanion from the abstraction of a proton on the methyl group on the isoxazole is then alkylated with the BOC protected bromomethlpiperidine (**60-6**) to give (**60-7**). (The preferential alkylation of the dianion on carbon over indolone nitrogen can be attributed to the greater nucleophilicity of the former.) The BOC protecting group is next removed by treatment with a strong acid. Akylation of the newly revealed piperidine nitrogen with benzyl bromide completes the synthesis of **icopezil** (**60-8**) [63].

A benzisoxazole moiety provides the nucleus of an anticonvulsant agent whose structure differs markedly from the traditional agents in this class. The synthesis starts with a compound (**61-1**) that incorporates a preformed benzisoxazole. Bromination proceeds on the position adjacent to the carboxylic acid (**61-2**). This intermediate loses carbon dioxide on heating, leaving behind the bromomethyl derivative (**61-3**). Displacement of the halogen with the ion from the reaction of imidazole with sodium hydride yields the alkylation product (**61-4**). The short side chain is then methylated by successive treatment with a base and methyl iodide to afford **zoniclezole** (**61-5**) [64].
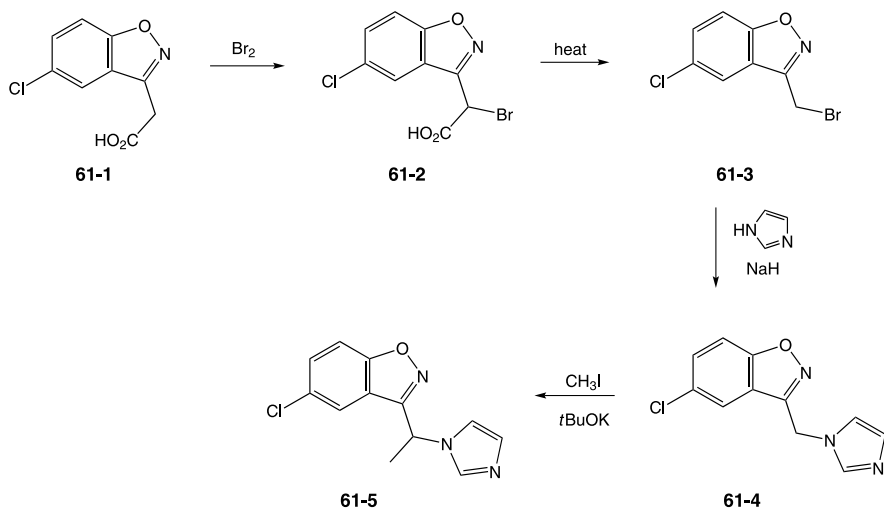
10.2.4. Benzothiazoles

Anthelmintic activity is retained when of one of the ring nitrogens in the 2-aminobenzimidazoles is replaced by sulfur. Treatment of the anilinothiol (**62-1**) with the thiocarbamoyl chloride from methyl urethane in the presence of triethylamine can be envisaged to yield the corresponding thioamide as the first intermediate, shown as its enol tautomer (**62-2**). Thiol exchange with the ring mercaptan will then close the ring to afford a benzothiazole. There is thus obtained the anthelmintic compound **tioxidazole** (**62-3**) [65].
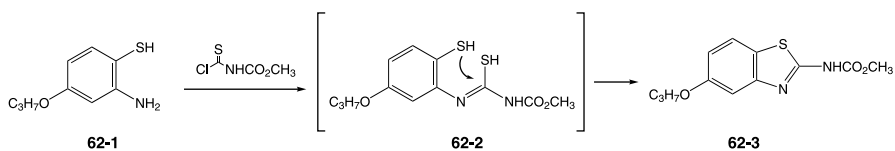
Replacement of the urethane carbonyl function by an aromatic ring leads to a benzo-thiazole that is described as an immune function modulator. In an analogous approach to that used above, anilinothiol (**63-1**) is condensed with the thiocarbamoyl chloride (**63-2**) again in the presence of a base. This leads directly to **frentizole** (**63-3**) [66].
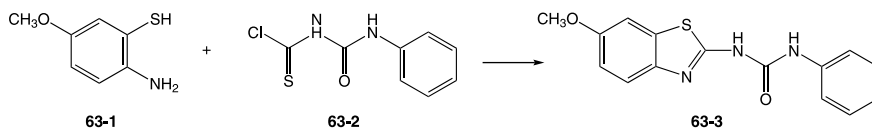
The presence of phosphorus is quite rare among therapeutic agents, despite its widespread occurrence in the various organic compounds involved in biochemical processes. This in fact represents an undeserved reputation of toxicity for phosphorus containing compounds based on the nerve gases and the phosphorus-based antitumor alkylating agent **cyclophosphamide**. The preparation of a phosphonate-containing benzothiazole is notable for the different strategy used for preparing the heterocyclic system. Reaction of the anilide (**64-1**) with phosphorus pentasulfide leads to the cor-responding thioamide (**64-2**). Potassium ferricyanide is a well-known oxidizing agent that has been used in natural product synthesis to bring about radical induced phenol coupling reactions. The reaction of (**64-2**) with that reagent, which probably proceeds by way of its enol, affords an analogous coupling product, the benzothiazole (**64-3**). The methyl group on the pendant benzene ring is then brominated with *N*-bromo-succinimide to give (**64-4**). Treatment of that compound with triethyl phosphite leads to the formation of the phosphonate (**64-5**) by way of the Arbuzov reaction. This product, **fostedil** (**64-5**) [67], is described as a calcium channel blocker that exhi-bits vasodilator activity.
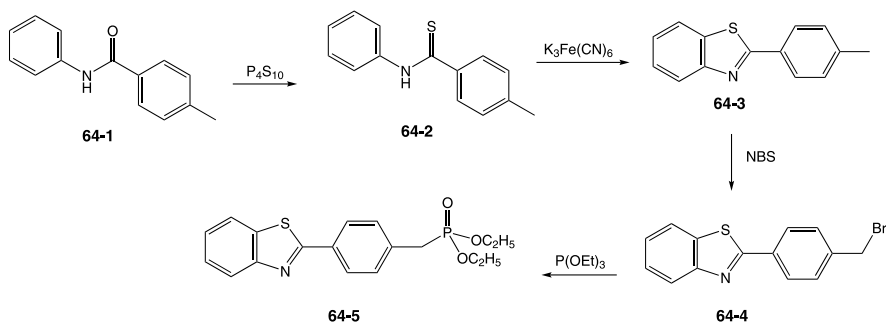
Dopamine and dopamine-like compound have been found to alleviate Parkinson's disease symptoms. One of the main problems in this treatment devolves about the difficulty of delivering compounds to the brain. A benzimidazole with a reduced

six-membered ring has been found to be useful in controlling Parkinson's disease symptoms; the drug was also unexpectedly approved for treating "restless legs syndrome." The synthesis starts by bromination of 4-acetamidocyclohexanone (**65-1**) to afford the mono-bromo derivative (**65-2**). In one of the classic methods for forming thiazoles, that intermediate is then allowed to react with thiourea to afford the fused thiazole (**65-3**). The amide is then cleaved and the resulting amine (**65-4**) resolved by diastereomeric salt formation. The S($-$) isomer is then acylated with propionic anhydride. Reduction of the amide (**65-5**) with diborane then affords the N-propyl derivative. There is thus obtained **pramipexole** (**65-6**) [68].
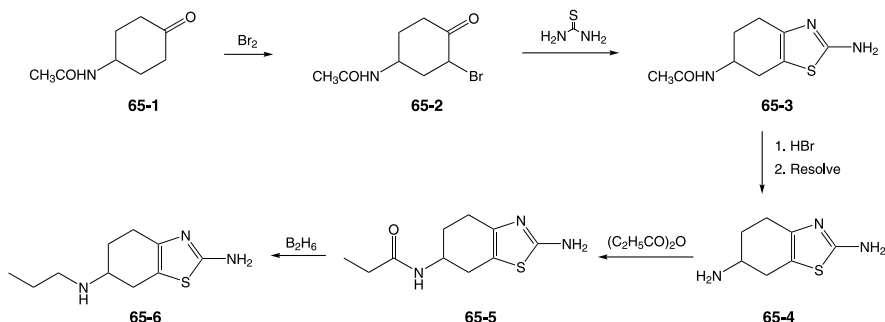
Alkylation of 2-aminobenzothiazole interestingly occurs on the ring nitrogen with a simultaneous shift of the double bond to the exocyclic position in neutral protic solvents. Thus, treatment of 6-chloroaminothiazole (**66-1**) with the complex chloroacetamide (**66-2**) leads to the 2-imino product of alkylation on ring nitrogen (**66-3**). Hydrolysis of that compound under acidic conditions gives the corresponding benzothiazol-2-one [69]. This product, **tiaramide** (**66-4**), is described as an antiasthmatic agent that also displays anti-inflamatory activity.

66-3, X = NH
66-4, X = O   HCl/CH₃OH
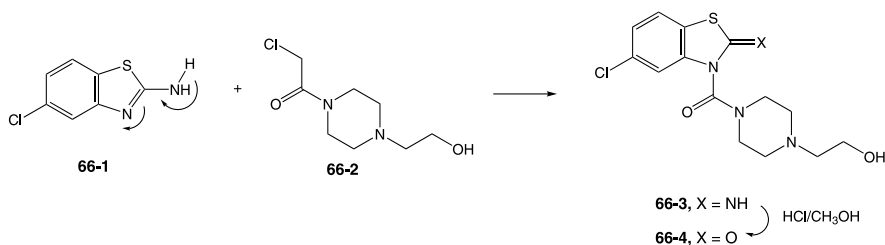
10.3. COMPOUNDS THAT CONTAIN THREE HETEROATOMS

A subcategory of dopamine receptor antagonists has found some use as antiemetic agents administered in conjunction with antitumor chemotherapy. The preparation of one of these agents based on a benzotriazole nucleus begins with nitration of the amino salicylate ester (**67-1**). Catalytic hydrogenation of the product (**67-2**) leads to the *ortho*-diamine (**67-3**). Treatment of this last product with nitrous acid

converts one of the amino groups to the corresponding diazonium salt. This then couples to the adjacent amine to afford the 1,2,3-fused triazole ring. Diazotization of either amine will lead to the same product due to the symmetry of the triazole. Ester interchange of (**67-4**) with the methylaminopyrrolidine (**67-5**) then affords the antiemetic agent **alizapride** (**67-6**) [70].
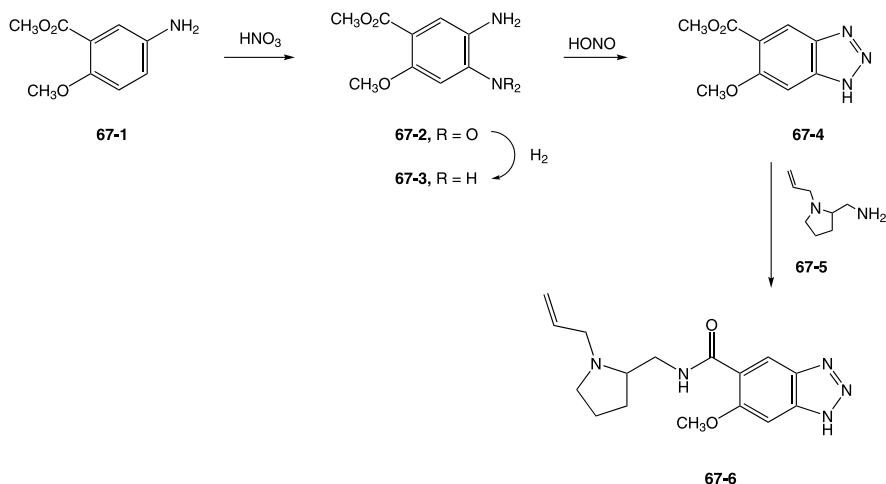
The antineoplastic aromatase inhibitors **anastrozole** and **letrozole** (Chapter 8) both incorporate a pair of cyano groups as well as a triazole ring. A related compound that retains the triazole as a ring fused to benzene but which lacks the nitriles retains aromatase blocking activity. Heating the nitrobenzoic acid (**68-1**) with methylamine leads to aromatic nucleopholic displacement of the highly activated chlorine. The resulting product (**68-2**) is then reduced catalytically to afford the diamine (**68-3**). This intermediate is converted to a fused triazole (**68-4**) much as above by reaction with nitrous acid. The carboxylate function is next taken on to an aldehyde (**68-5**)
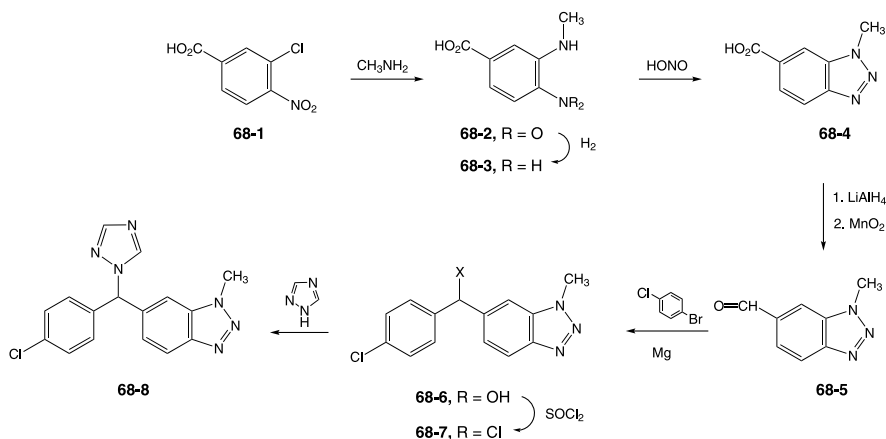
by successive reduction to the benzyl alcohol followed by back-oxidation with manganese dioxide (**68-6**). Treatment of the carbinol with thionyl chloride converts the carbinol to the corresponding chloride (**68-7**). Displacement of the halide with 1,2,4-triazole completes the synthesis of **vorozole** (**68-8**) [71].

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CHAPTER 11

SIX-MEMBERED HETEROCYCLES FUSED TO A BENZENE RING

11.1. COMPOUNDS THAT CONTAIN ONE HETEROATOM

11.1.1. Coumarins

Epidemiological investigations in the 1930s of outbreaks of cattle deaths due to hemorrhaging led to the identification of spoiled sweet clover as the causative agent. The natural product isolation and structural elucidation studies that followed unambiguously pointed to the condensation product (**1-1**) between coumarin and formaldehyde as the cause of those deaths. This was confirmed by the finding that this compound, now known as **dicoumarol**, is a potent inhibitor of blood coagulation in mammalian species. It has subsequently been established that this agent and its congeners inhibit the synthesis in the liver of a series of peptide factors involved in the intricate blood clotting cascade; this accounts for their lack of efficacy *in vitro*.

Anticoagulants play an important role in post-surgical recovery by preventing wound-induced thrombus formation. **Dicoumarol** has now been largely superseded in clinical use by an analogue that contains but a single coumarin moiety. The shorter biological half-life of this agent, **warfarin** (**1-6**) allows more accurate control of blood levels and thus a better chance of avoiding the danger of hemorrhaging due to elevated clotting times. Both compounds, it might be noted, have also been extensively used as rat toxins. The generic name, **warfarin**, alludes to the fact that the drug was developed at the Wisconsin Alumni Research Foundation (WARF), an organization that was itself initially funded by patent royalties from the Steenbock process for increasing vitamin D activity in milk by ultraviolet (UV) irradiation.

The succinct synthesis of warfarin starts with condensation of *ortho*-hydroxy-acetophenone (**1-2**) with ethyl carbonate to give the β-ketoester (**1-3**) as the presumed intermediate shown in the enol form. Attack of the phenoxide on the ester grouping will lead to cyclization and the formation of the coumarin (**1-4**). Conjugate addition of the anion from that product to methyl styryl ketone (**1-5**) gives the corresponding Michael adduct and thus **warfarin** (**1-6**) [1].
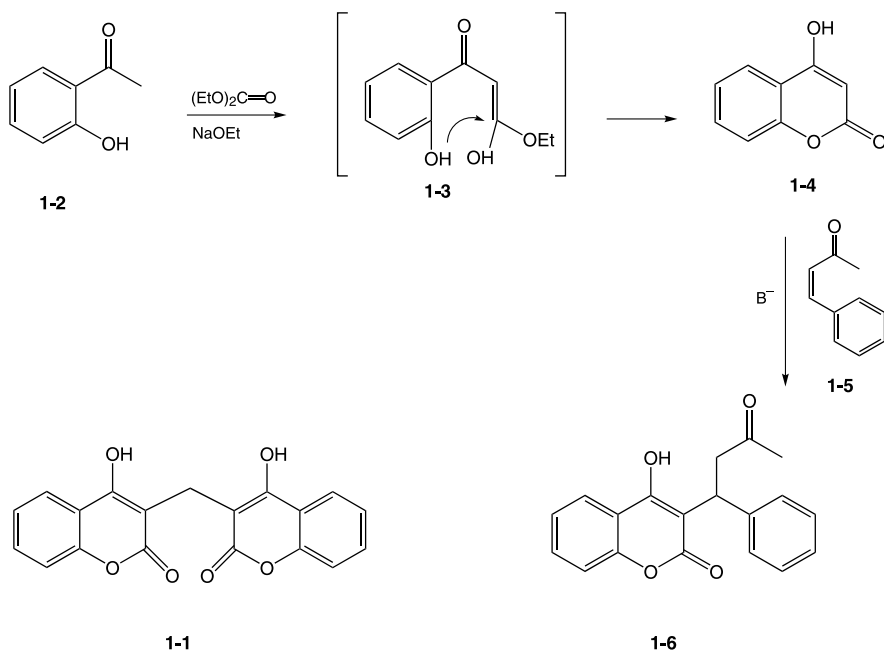
A somewhat more complex coumarin that includes basic nitrogen has been used as a coronary vasodilator. The key reaction in the synthesis of this compound involves Friedel–Crafts-like reaction of the alkylation product (**2-1**) from ethyl acetoacetate
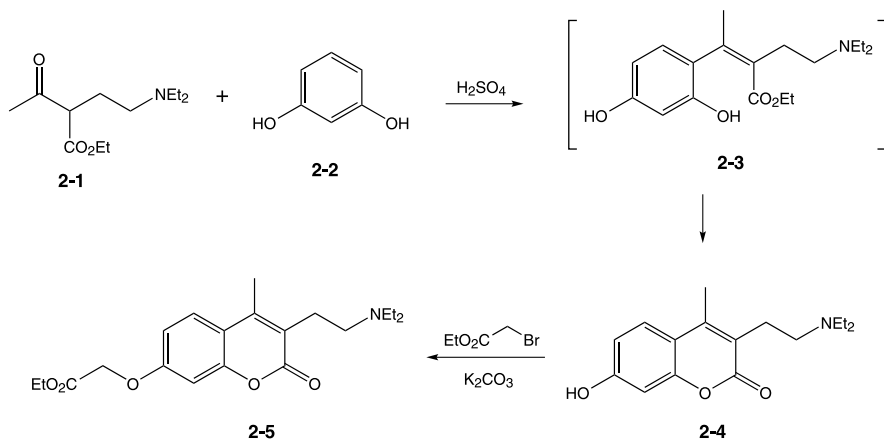
with 2-chlorotriethylamine with resorcinol to give initially an acylation such as (**2-3**) (no stereochemistry implied). This then cyclizes to the coumarin (**2-4**) under reaction conditions. The remaining free phenolic group is then alkylated with ethyl bromoacetate to give the corresponding ether and thus **chromonar** (**2-6**) [2].

Recognition of the photosensitizing effect of the naturally occurring furanocoumarin psoralin (desmethoxy (**3-6**)) led to trials of its utility for the treatment of skin diseases such as psoriasis. The partial effectiveness of this compound led to the preparation of synthetic analogues. The two commercially available drugs, **methoxsalen** (**3-8**) and **trioxsalen** (**4-6**), are used in a procedure that goes by the acronym PUVA (psoralen and UVA irradiation) for the treatment of psoriasis and other skin diseases.

The preparation of the first of these compounds starts with phosphorus oxychloride-mediated acylation of pyrogallol, (**3-1**) with chloroacetic acid to give the chloromethyl ketone (**3-2**). Treatment of that intermediate with potassium carbonate leads to the displacement of halogen by the phenoxide and the formation of a benzofuranone ring. The carbonyl group is then reduced catalytically to methylene to afford the benzodihydrofuran (**3-3**). That product is then allowed to react with malic acid (**3-4**) in concentrated sulfuric acid. The overall reaction can be viewed as involving the initial decarboxylation of (**3-4**) to give formylaceric acid (**3-5**). The enol from the latter then attacks the highly activated aromatic ring to give the cinnamic acid derivative (**3-6**) (no stereochemistry implied). Internal esterification then completes formation of the coumarin and yields (**3-7**). The remaining free phenolic group is then treated with diazomethane and the resulting methyl ether dehydrogenated over palladium on charcoal. There is thus obtained **methoxsalen** (**3-8**) [3].
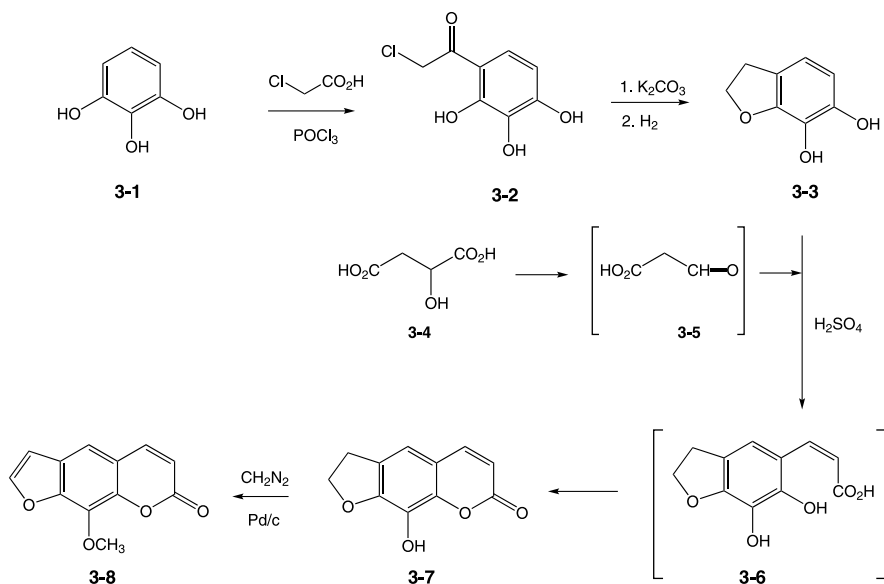
The strategy used to prepare the analogue, **trixosalen** (**4-6**), differs in the order in which the heterocyclic rings are built. Condensation of malonic acid and substituted

acetophenone (**4-1**) probably proceeds to initially give the malonylidene compound from a Knoevnagel-like reaction with the carbonyl group. This cyclizes to the coumarin (**4-2**) under reaction conditions. The superfluous carboxyl group is then caused to decarboxylate by heating to afford (**4-3**) [4]. Reaction of that intermediate with 2,3-dibromoethylene first affords the simple *O*-allyl ether (**4-4**). That then undergoes electrocyclic Claisen rearrangement to the *C*-allylated derivative (**4-5**). Heating that product in a high boiling basic solvent such as diethylaniline results in the displacement of bromine by alkoxide and the formation of a furanylidene ring. The double bond then shifts into the ring to afford a furan and thus **trioxsalen** (**4-6**) [5].
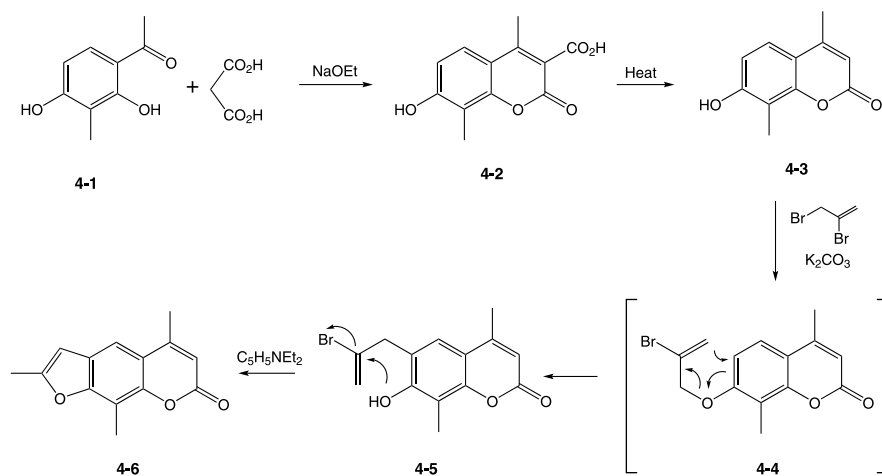
11.1.2. Chromones

The chromone **cromolyn sodium** (**5-5**) was at one time considered the forerunner of a novel class of antiallergic and antiasthmatic drugs that act at one of the earliest stages of the allergic reaction. Detailed experiments, actually conducted after the drug's clinical effectiveness had been confirmed, suggested that the compound inhibited the release of mediators of the allergic reaction from mast cells. The drug is not very active when taken orally and is usually applied topically to the lung by insufflation as its sodium salt. Considerable efforts to uncover additional structurally related mediator release inhibitors have had only limited success.

   The preparation starts much as does that of β-blockers, by reaction of the phenol (**5-1**) with epichlorohydrin with the important difference that the reaction is conducted with a controlled amount of the epoxide. The initially formed glycydil ether (**5-2**) thus reacts with a second phenoxide ion to afford the double ether of glycerol (**5-3**). This product is then condensed with diethyl oxalate in the presence of a base. The initially formed acylation product (**5-4**) then undergoes internal hydroxyl exchange to form a coumarone ring. The structure shown for the initial

adduct is presented for illustrative reasons only; the sequence is just as likely to proceed by stepwise addition-cyclization of the two halves of (**5-3**). Saponification of the product, without the usual neutralization step, affords **cromolyn sodium (5-5)** [6].
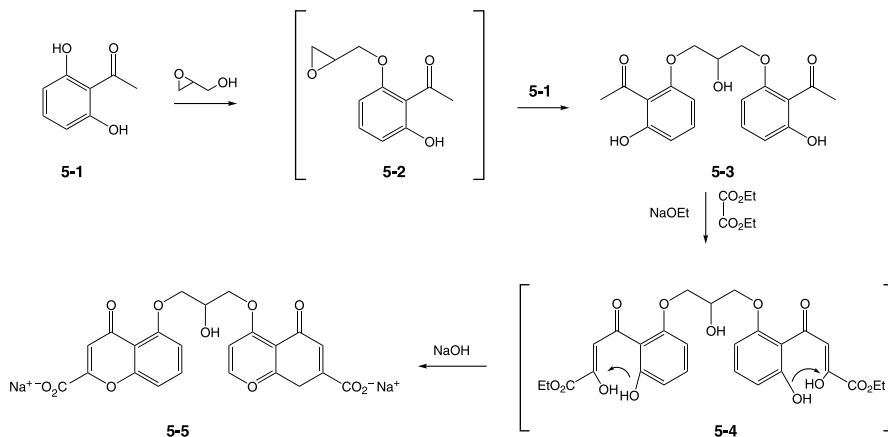
The Kostanecki reaction, which involves the esterification of *ortho* and acylphenol followed by aldol cyclization of the resulting ketoester, provides a convenient entry to chromones. As a matter of passing interest, the subclass of 2-phenyl derivatives obtained by use of benzoyl chloride is named flavones. Thus, reaction of dihydroxy-propiophenone (**6-1**) with benzoyl chloride in the presence of sodium benzoate can be visualized as involving an initial formation of the ester (**6-2**). Internal condensation of this dicarbonyl derivative, which can proceed in only one direction, provides a new ring and results in the flavone (**6-3**). The remaining free phenolic group is then converted to its methyl ether (**6-41**) by means of dimethyl sulfate. Reaction with formaldehyde in the presence of dry hydrogen chloride serves to introduce a chloromethyl group (**6-5**), interestingly at the more hindered position. The displacement of chlorine by dimethylamine affords the respiratory stimulant **dimefline (6-6)** [7].
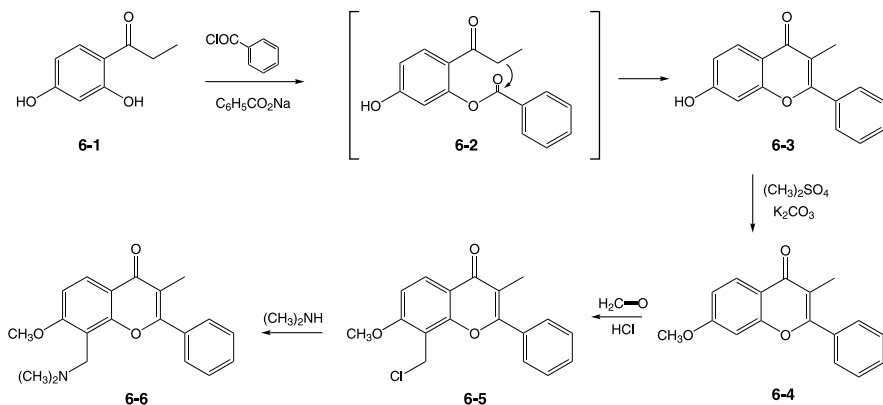
Nitration of hydroxypropiophenone (**7-1**) followed by conversion of the phenol to its methyl ether by means of methyl iodide provides the intermediate (**7-2**); the nitro group is then reduced to the corresponding amine (**7-3**) by catalytic reduction. The newly introduced amine is then replaced by a nitrile group by successive conversion to the diazonium salt by means of nitrous acid followed by treatment with cuprous cyanide (**7-4**). Reaction with aluminum chloride removes the methyl ether to afford the *ortho* acylphenol (**7-5**). This is converted to the chromone (**7-6**) as above by reaction with benzoyl chloride and sodium benzoate. The nitrile is next hydrolyzed to the carboxylic acid (**7-7**) by means of sulfuric acid. The acid is then converted to its acid chloride by means of thionyl chloride and that treated with 2-(*N*-piperidyl)ethanol (**7-8**). There is thus obtained **flavoxate** (**7-9**) [8], a muscle relaxant whose name reflects its flavone nucleus.
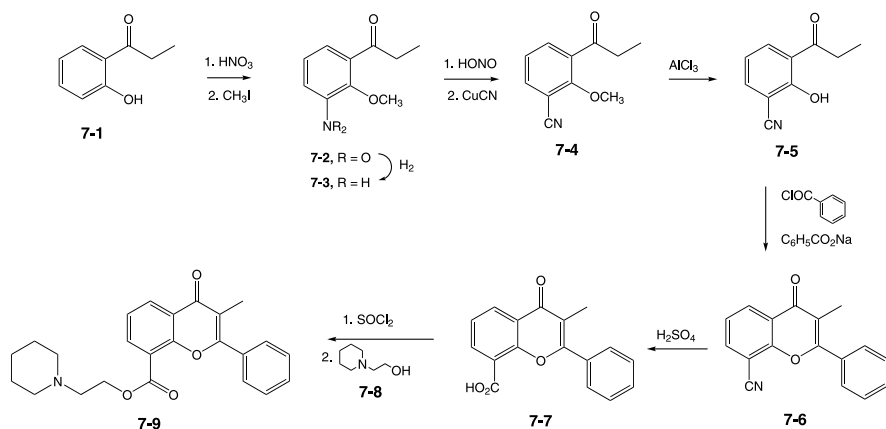
The extremely wide structural latitude for the aromatic nucleus for β-blockers has been noted repeatedly. Though the antihypertensive agent **flavodilol** (**8-2**) is seemingly yet one more contributor to that theme, the compound seems not to interact with β-adrenergic receptors. This agent is obtained by subjecting (**8-1**) to the standard glycidyl ether formation with epichlrohydrin followed by opening of the oxirane with propylamine [9].
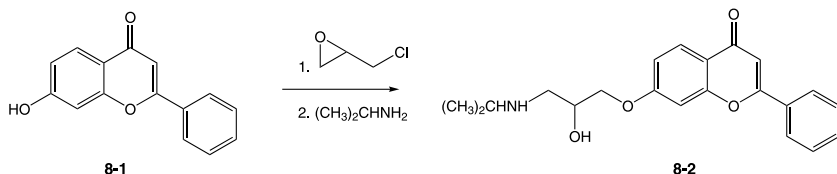
Apoptosis, the mechanism that times the lifetime of individual cells, is disrupted in neoplasms and largely accounts for their immortality. The benzopyran **alvocidib** (**9-7**), originally known as **flavoperidol**, has shown promising activity as an agent that restores apoptosis. In the absence of a direct reference, the scheme shown here is based on that for the compound in which methyl replaces the pendant chlorophenyl

ring [10]. The sequence starts with the addition of diborane to the olefin in the tetrahydropyridine (**9-1**), itself available by addition of an organometallic reagent to *N*-methyl-4-piperidone followed by dehydration of the tertiary alcohol. Oxidation of the hydroborane adduct with a peroxide then affords the hydration product as its *cis* isomer (**9-2**). The stereochemistry at that center is then reversed by oxidation to the corresponding ketone, followed by reduction with sodium borohydride (**9-3**). That intermediate is then acylated with acetic anhydride in the presence of boron trifluoride. Using an excess of the latter reagent leads to selective demethylation of the ether adjacent to the newly introduce acyl function (**9-4**). Claisen condensation of that product with methyl 2-chlorobenzoate would then afford the β-diketone (**9-5**). Treatment with acid causes the phenolic oxygen to add to the enone, thus forming the pyran ring by an addition-elimination sequence (**9-6**). Demethylation of the remaining phenolic ethers, for example with boron tribromide, would then afford alvocidib [11] (**9-7**).
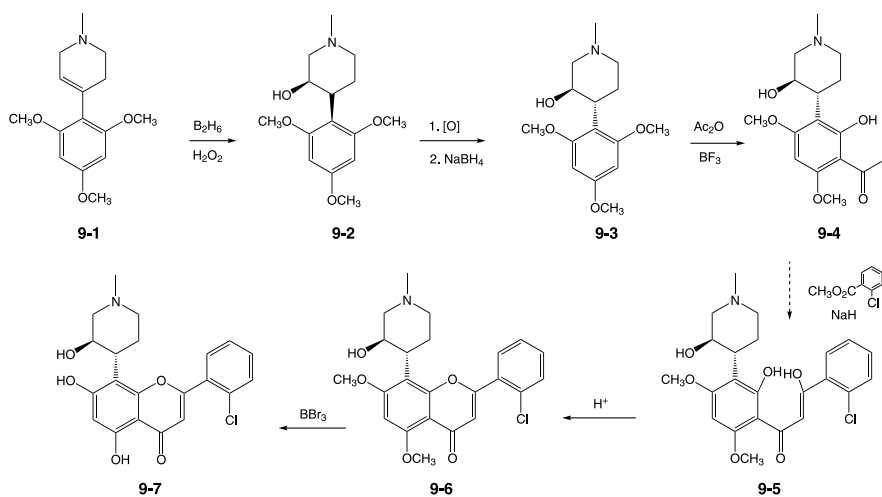
11.1.3. Benzopyrans

The well-known active principle of marijuana, tetrahydrocannabinol, THC (**10-1**), exhibits a wide spectrum of activities in the CNS, the most notable of which is its euphoriant and hallucinogenic effects. The bruited antiemetic activity of the drug has led to its limited approval for that use in special situations as well as to endless controversy. A synthetic analogue has been investigated clinically for that indication. Like the classical syntheses of the natural product itself [12], the route to the analogue also involves the coupling of a terpene with a resorcinol derivative as a key step. The starting enol acetate (**10-2**) is obtained by treatment of nopinone, itself available by oxidation of the natural product β-pinene, with acetic anhydride. Oxidation with lead tetraacetate leads to the acetic acid acetal (**10-3**) of the dehydrogenated ketone. Reaction of that with resorcinol derivative (**10-4**) in

the presence of toluenesulfonic acid leads to the alkylation of the aromatic ring and the formation of the coupling product (**10-5**). The oxonium ion formed by treatment of that intermediate with the strong Lewis acid, stannic chloride, then attacks the quaternary center on the bicyclic fused cyclobutane ring from the back side; this forms the new pyran ring while at the same time opening the strained four-membered ring. The *trans* stereochemistry of the new ring fusion in the product, **nabilone** (**10-6**), follows from the stereochemistry of the starting material and the direction of attack [13].
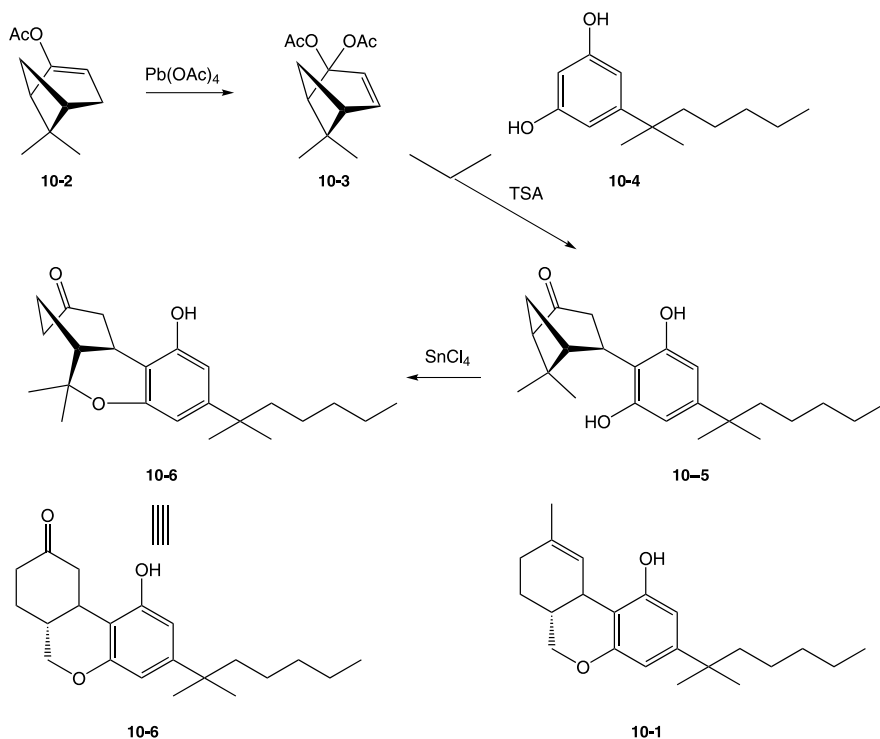
Many of the leukotriene antagonist antiallergic compounds consist of long chain acids that bear a passing resemblance to the fatty chains of the leukotrienes (see Chapter 1). A tetrahydrobenzopyran ring system provides the nucleus for one of these antagonists. The requisite ring system is formed by reaction of the dihydroxy-acetophenone (**11-1**) with ethyl oxalate in the presence of a strong base; formation of the chromone (**11-2**) follows an analogous course to that outlined for **cromolyn**. Exhaustive hydrogenation reduces both the double and the carbonyl groups to afford (**11-3**). Acylation with acetyl chloride in the presence of aluminum chloride then affords the ketone (**11-4**). The free phenol in the product is next alkylated with 5-acetoxy-1-bromopentane; the ester is then saponified and the resulting alcohol converted to its mesylate by reaction with methanesulfonyl chloride (**11-5**); the ester on the heterocycle is cleaved in the process. Displacement of that good leaving group with the alkoxide from the complex resorcinol derivative (**11-6**)

results in the formation of the ether from the nonchelated phenolic group at the ring position *para* to the carbonyl group. There is thus obtained **ablukast (11-7)** [14].
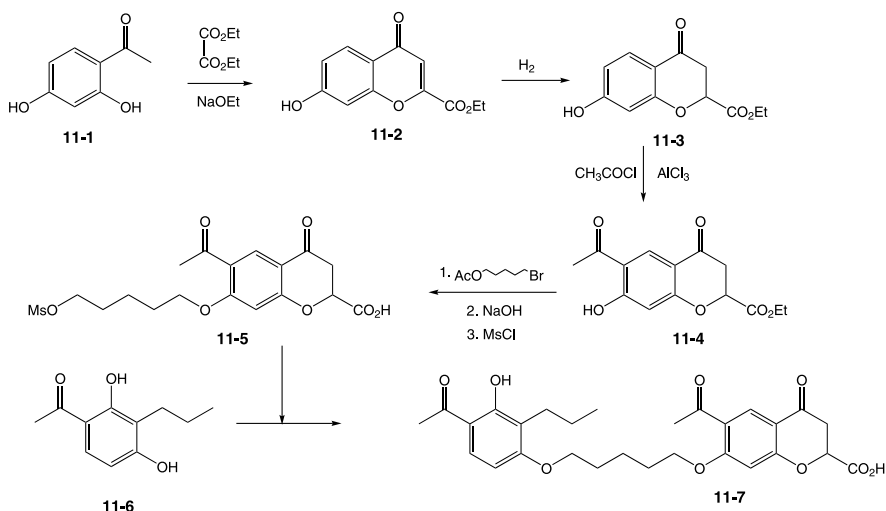
The cataracts that can appear even in those diabetics whose disease is under control have been attributed to accumulation in the eye of sorbitol that results from the reduction of glucose by elevated levels of the enzyme aldose reductase that accompanies the disease. Inhibitors of that enzyme have been investigated as a means for controlling such cataracts. Known agents, as would be expected with enzyme inhibitors, tend to show marked differences in potency between optical isomers. The enantioselective synthesis of one of these compounds starts with the formation of an imine (**12-3**) of dihydrochromone (**12-1**) with the *S* form of the chiral
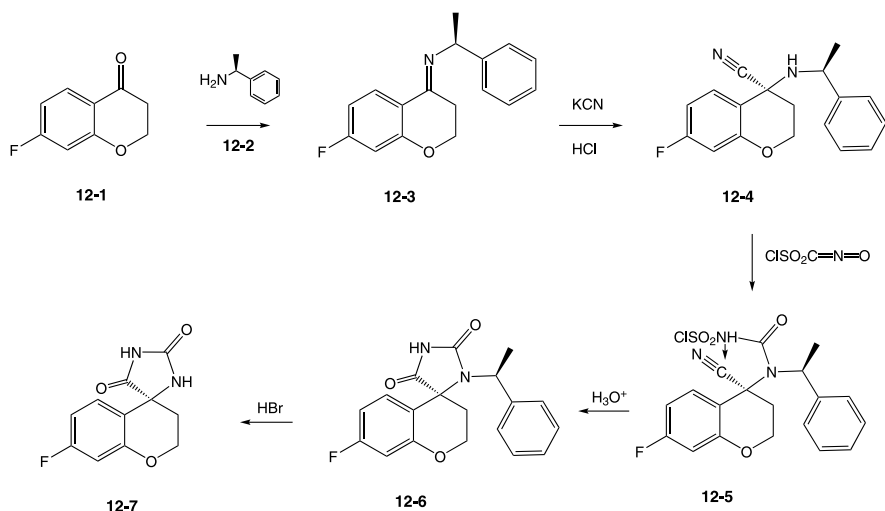
auxiliary α-methylbenzylamine (**12-2**). That reagent will also provide one of the nitrogen atoms required in the final molecule. Reaction of the imine with hydrogen cyanide leads to the formation of the α-aminonitrile (**12-4**); the adjacent chirality leads to the formation of that derivative as a single enantiomer. The remaining two carbons for the spirocyclic ring are then incorporated by addition of chlorosulfony-lisocyanate to form the derivatized urea (**12-5**). Reaction with hydrochloric acid leads to a loss of the chlorosulfonyl group with a consequent addition to the nitrile of the thus-revealed terminal primary amide group. The first-formed imine hydro-lyzes in the reaction mixture to afford the spirocyclic hydantoin (**12-6**). Treatment with hydrogen bromide cleaves the benzylic bond, causing a loss of the phenethyl moiety and affording **sorbinil** (**12-7**) as a single enantiomer [15].

A structurally unusual β-blocker that uses a second molecule of itself as the substituent on nitrogen is included here in spite of the ubiquity of this class of compounds. Exhaustive hydrogenation of the chromone (**13-1**) leads to a reduction of both the double bond and the carbonyl group, as in the case of (**11-2**). The car-boxylic acid is then reduced to an aldehyde (**13-2**) by means of diisobutylaluminum hydride. Reaction of that intermediate with the ylide from trimethylsulfonium iodide gives the oxirane (**13-3**) via the addition-displacement process discussed earlier (see Chapters 3 and 8). Treatment of an excess of that epoxide with benzylamine leads to the addition of two equivalents of that compound with each basic nitrogen (**13-4**). The product is then debenzylated by catalytic reduction over palladium to afford **nebivolol** (**13-5**) [16]. The presence of four chiral centers in the product predicts the existence of 16 chiral pairs.
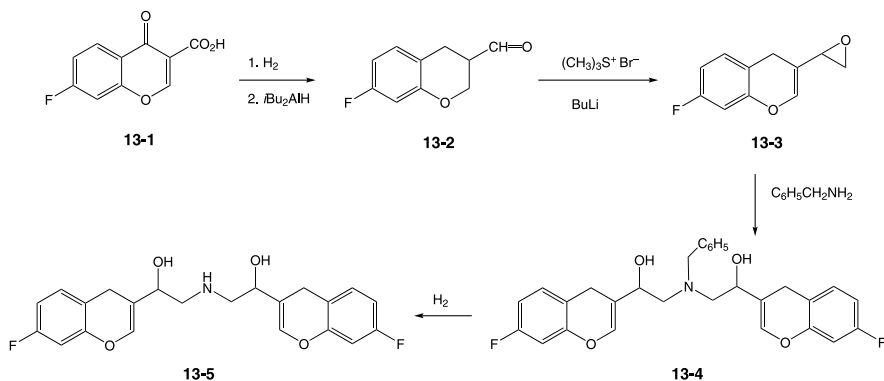
The sizeable number of serotinergic drugs for treating migraines noted in the preceding chapter all incorporate the indole nucleus found in serotonin itself. It is thus of interest that a compound based on a benzopyran manifests much the same activity. Alkylation of phenol with 2-bromobutyrolactone (**14-2**) leads to the ether (**14-3**). Oxidation of that product with chromium trioxide then leads to the substituted succinic anhydride (**14-4**). Treatment of anhydride with polyphosphoric acid leads to the acylation of the aromatic ring and the formation of the benzopyranone ring (**14-5**). The carbonyl group is then selectively reduced by any of several methods, as, for

example, conversion to a thioacetal followed by reductive de-sulfurization with nickel (**14-6**). The carboxylic acid is next reduced to the corresponding aldehyde (**14-7**) by successive conversion to an acid chloride followed by hydrogenation in the presence of thiophene. A second hydrogenation in the presence of benzylamine leads to the reductive alkylation product (**14-8**). Reaction of that product with acrylonitrile leads to a conjugate addition to the amino group and the formation of (**14-9**). Reduction of the nitrile affords the diamine (**14-10**). Reaction of this last diamine with tetrahydropyrimidine chloride (**14-11**), itself formed by treatment of pyramid-2-one with phosphorus oxychloride, leads to the displacement of halogen by the terminal, and thus more accessible, amino group in (**14-10**). There is thus formed the serotinergic agent **alnitidan** (**14-12**) [17].
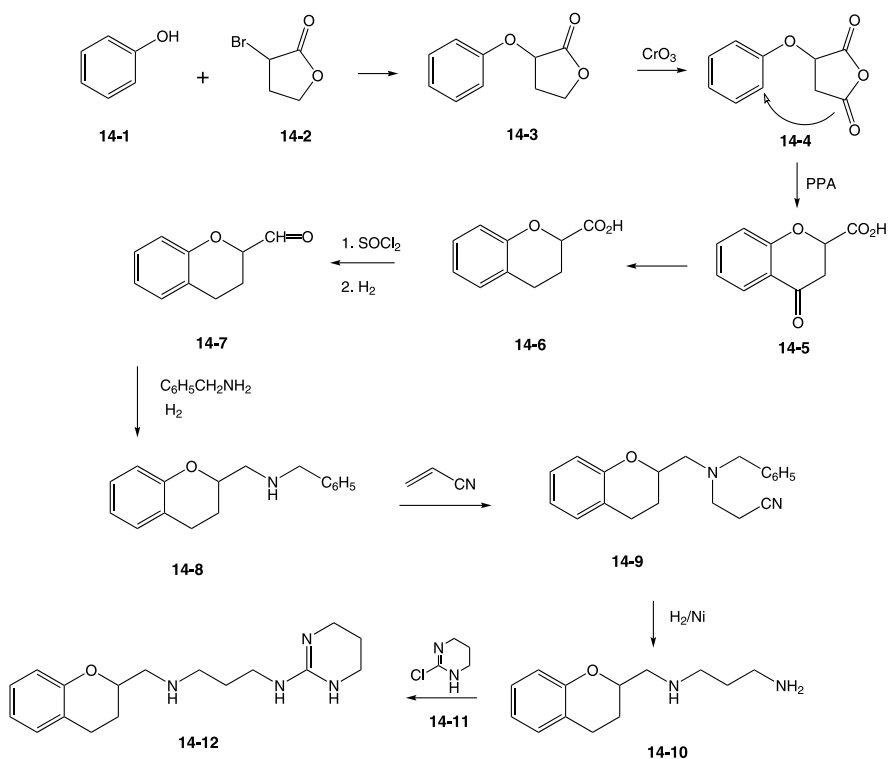
A benzoisopyran provides the nucleus for an appetite-suppressing agent that incorporates in its structure a significant portion of the prototype anorexigenic agent, amphetamine. Carefully controlled reduction of the lactone (**15-1**) with diisobutylaluminum hydride leads to the lactol (**15-2**). This is then treated with nitro-methane in the presence of a strong base. The carbanion reacts with the open form of the lactol (**15-3**) to give first the aldol product (**15-4**). The benzylic hydroxyl group in that intermediate then adds to the strongly electrophilic olefin to re-form the benzoiso-pyran ring (**15-5**). Catalytic reduction of the nitro group leads to the primary amine and thus **fenisorex** (**15-6**) [18].
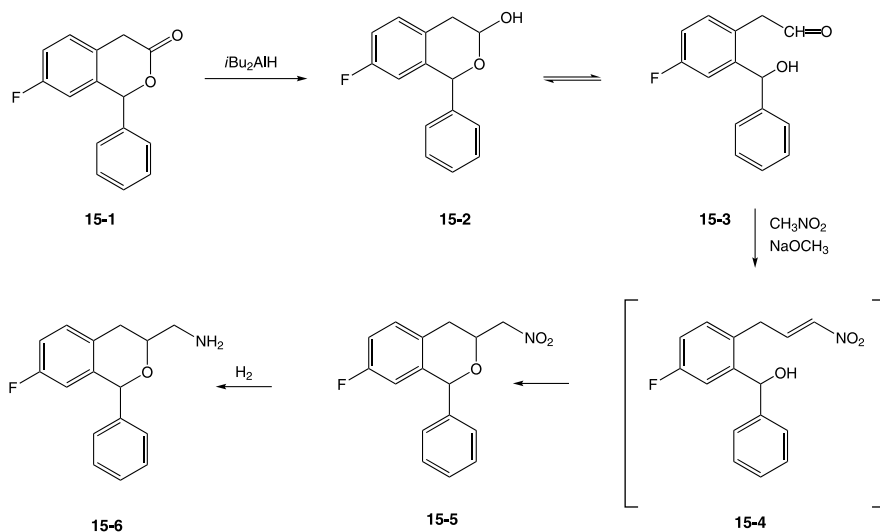
11.1.4. Quinolines

11.1.4.1. Antimalarial Compounds. Malaria constitutes one of the most wide-spread infectious diseases in humans; over 270 million new infections and 2 million deaths from the disease are estimated to occur worldwide each year. The causative pro-tozoan plasmodia, comprised largely of the species *falciparum* and *vivax*, undergo a complex life history cycling between mosquitoes and vertebrates as hosts. This multi-plicity of forms complicates approaches to chemotherapy. In spite of the fact that this is one of the earliest recorded human diseases, the role of the *anopheles* mosquito as the infecting agent was not recognized until 1898. Some progress was made in control-ling the disease in the immediate post-World War II period, particularly in the United States through mosquito control using the now-banned insecticide DDT. The first and still widely used drug for treating this disease comes from the adventitious finding of the antimalarial activity of cinchona bark in the early seventeenth century. The active drug, **quinine** (**16-1**), forms the major part of the 25 alkaloids found in cinchona bark. The compound was isolated in pure crystalline form by Pelletier in 1820. The relatively complex structure was not determined until 1907.

16-1
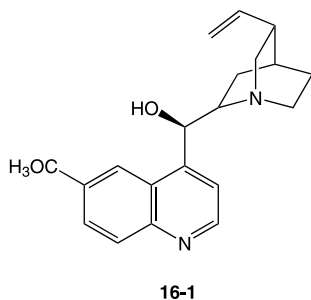
The complexity of the structure was mitigated against the synthesis of the compound itself or closely related analogues. Investigations instead concentrated on examination as potential antimalarial drugs of simplified synthetic compounds whose structures bore some relation to that of quinine. A sizeable group of antimalarial compounds is thus based on the quinoline nucleus that forms a major part of the structure of quinine. The first antimalarials were prepared in Germany in the 1930s in anticipation of the coming war. A large program was started in the United States after Japan had seized sources of quinine at the beginning of that war. The high frequency with which a quinoline or quinoline-like moiety occurs in candidates prepared in that massive random screening program is probably due more to bias toward compounds that include a fragment present in quinine than to systematic molecular dissection. Two of the more important early synthetic antimalarial drugs, **quinacrine** and **methacrine**, are in fact based on an acridine nucleus that consists of a quinoline with an added fused benzene ring; the discussion of these two compounds is deferred to Chapter 13. One of the classical entries to 4 substituted quinolines involves the condensation of an aniline with a 1,3-dicarbonyl fragment. Reaction of diethyl 2-ketoglutarate, shown as its enol tautomer (**17-2**) with 3-chloroaniline (**17-1**), leads to the imine (**17-3**). Heating that compound in a high boiling solvent leads to the displacement of an ethoxyl fragment from the ester with consequent cyclization (**17-4**); saponification of the product leads to the acid (**17-5**). Heating that intermediate leads to a loss of the carboxyl group; the enol group at the 4 position is then converted to the chloride (**17-6**) by the now-familiar reaction with phosphorus oxychloride. The displacement of halogen by the primary amine in 2-amino-5-(diethylamino)pentane leads to the very widely used antimalarial compound **chloroquine** (**17-7**) [19]; the utility of this drug is threatened by the increasing development of resistant strains of plasmodia.
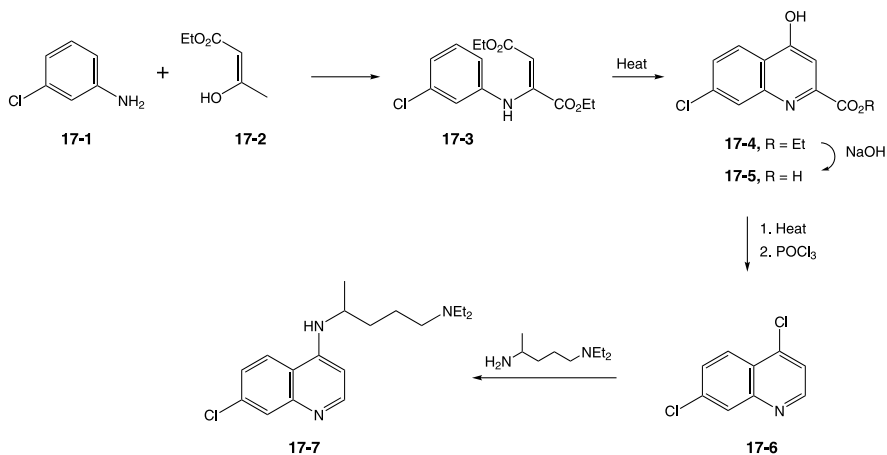
The starting quinoline (**18-2**) for analogues that include a methyl group at the 3 position is prepared by a modification of the scheme that consists of using ethyl

3-methyl-2-ketoglutarate, (**18-1**) as a starting material. Alkylation of (**18-2**) with 2-amino-5-(diethylamino)pentane yields **sontoquine** (**18-3**) [20].
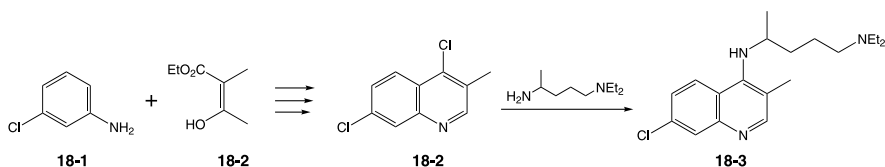
The inclusion of aromatic rings as part of the side chains results in quite potent agents, possibly because the rigid rings better define the position of the basic nitrogen. Reaction of *para*-hydroxyacetanilide (**19-1**) with formaldehyde and diethylamine affords the corresponding Mannich product (**19-2**); hydrolysis of the acetamide then leads to the aniline (**19-3**). Treatment of that compound with dichloro-quinoline (**17-6**) leads to the displacement of chlorine on the heterocyclic ring and the formation of **amodiaquine** (**19-4**) [21].
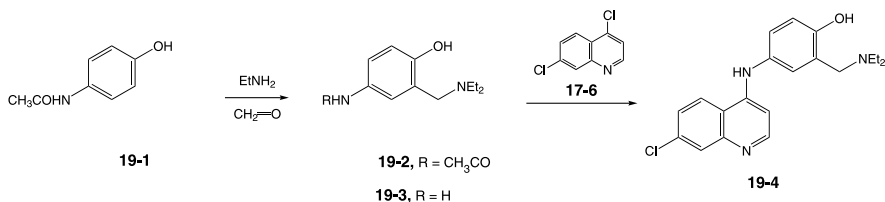
In a closely related example, a Mannich reaction of the somewhat more complex phenol (**20-1**) with formaldehyde and *tert*-butylamine gives the aminomethylated product (**20-2**). Hydrolysis of the acetamide protecting group then affords the corresponding aniline (**20-3**). Alkylation with the quinoline (**17-6**) in this case also proceeds on aniline nitrogen. The selectivity over the more basic secondary side nitrogen can probably be ascribed to steric hindrance about the latter. There is thus obtained **tebuquine** (**20-4**) [22].
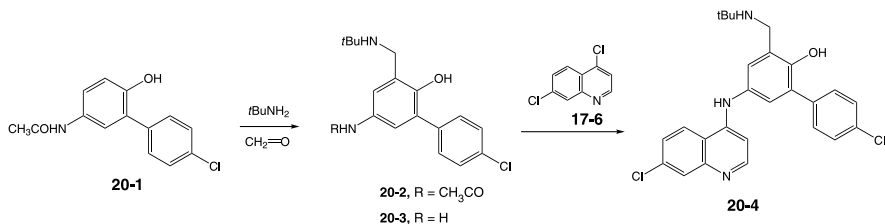
The first synthetic quinoline antimalarial agent interestingly carried the basic side chains at the 8 rather than the 4 position, as in quinine, lending further credence to the

origin of the structures of these compounds from random screening instead of molecular dissection programs. The starting quinoline (**21-3**) is in this case obtained by reaction of substituted aniline (**21-1**) with glycerol in sulfuric acid and nitrobenzene. It is known that the first step consists of oxidation and dehydration of glycerol to acrolein. Studies on the mechanism of the quinoline synthesis from unsaturated carbonyl compounds and anilines (Skraup reaction) suggest that the first intermediate consists of a Michael-like adduct such as (**21-2**). This cyclizes to a dihydroquinoline under the strongly acidic conditions; the presence of oxidants leads to the aromatization of the heterocyclic ring to give quinoline (**21-3**). The nitro group is then reduced to an amine (**21-4**) by any of several means such as, for example, hydrogenation. Reductive alkylation of that primary amino group with 1-diethylaminopentan-4-one gives the antimalarial drug **pamaquine** (**21-5**) [23].
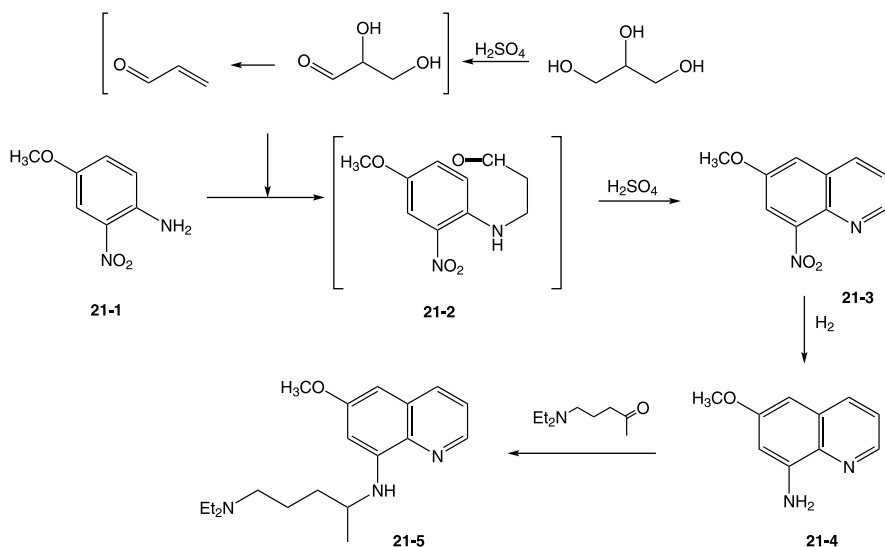
A more recently introduced antimalarial drug, the product of a U.S. Army sponsored program at Walter Reid Medical Center, represents a return to the structure of **quinine** as the model in that the basic nitrogen is connected to the quinoline at a hydroxymethyl group at position 4 on the quinoline ring. The unexpectedly long half-life of this drug, **mefloquine** (**22-7**), in serum, 385 ± 150 hours [24] (16 days!) permits a dosage regime that consists of a single oral tablet taken at weekly intervals. A very concise synthesis starts with the displacement of bromine in 5-bromohexene (**22-1**) by potassium phthalimide to give the protected amine (**22-2**). Palladium mediated coupling of the olefin with the substituted 4-bromoquinoline (**22-3**) affords the vinylation product (**22-4**). The double bond is then oxidized to the corresponding epoxide (**22-5**) with peracid. The phthalimide protecting group is next removed in the usual way by treatment with hydrazine to afford the transient primary amine (**22-6**). This function then opens the oxirane, with the consequent

formation of a piperidine ring; opening via the alternate epoxide bond is disfavored since it would lead to a seven-membered ring. There is thus obtained the antimalarial drug **mefloquine** (**22-7**) [25].
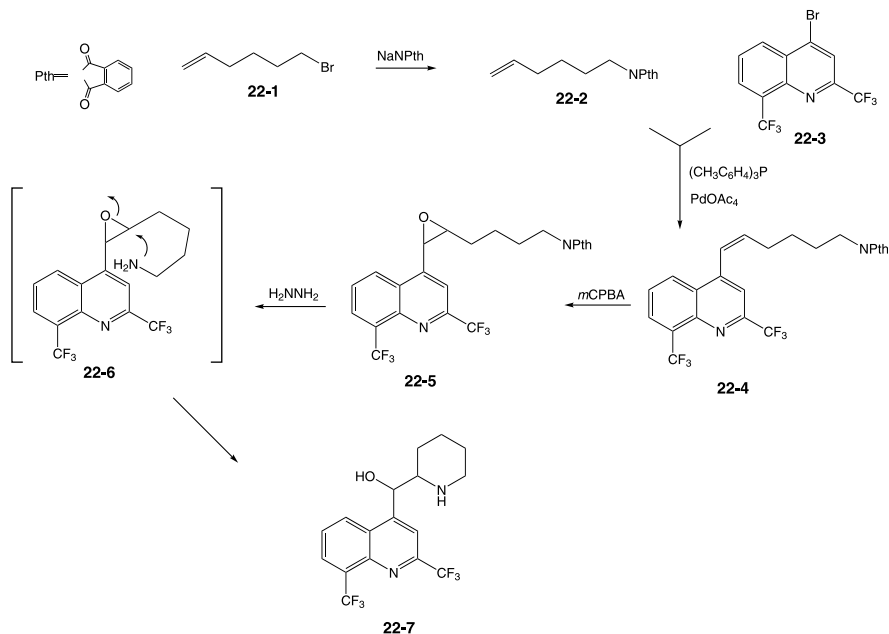
11.1.4.2. Other Quinolines. The quinoline nucleus also appears in many of the compounds that have activity against other parasitic protozoa and amoeba. The 7,8-dialkoxy-4-hydroxyquinoline-carboxylates, for example, comprise an important class of drugs that are toxic to coccidia, a protozoan that can devastate commercial poultry flocks. The structures of these compounds interestingly foreshadow the wide-spectrum quinolone "acin" antibiotics discussed below. Compounds within the cocciodostatic series vary mainly in the nature of the substituents on the oxygen atoms on the carbocyclic ring. The key step in the syntheses of these agents is the formation of the quinoline ring. A typical example involves the addition to diethyl ethoxymethylenemalonate (EMME) of the *bis-iso*-butylalkoxyaniline (**23-1**), obtained by reduction of the nitration product from the catechol ether; elimination of the ethanol affords the adduct (**23-2**). Heating that compound in a high boiling ether such as Dowtherm leads to cyclization by displacement of ethoxide and the formation of a transient quinolone; this spontaneously enolizes to the hydroxyquinoline **buquinolate** (**23-3**) [26].

The reaction follows the same course when one of the alkoxy groups in the starting material is replaced by alkyl. Thus, condensation of aniline (**23-4**) with EMME

followed by heating of the product (**23-5**) in Dowtherm leads to the poultry coccidiostat **nequinate** (**23-6**) [27].
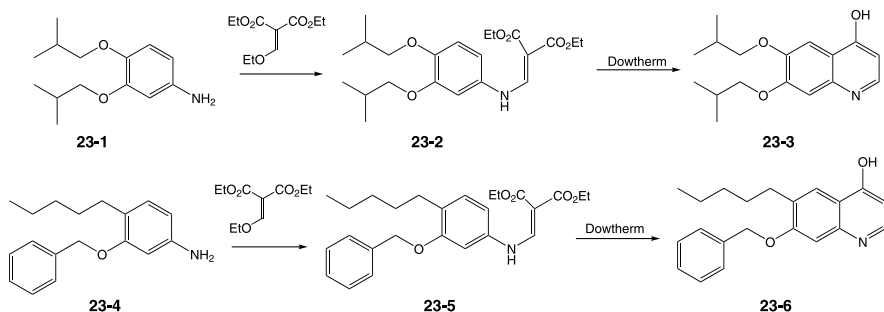
The antiprotozoal spectrum is apparently changed by replacing the alkoxy substituent by nitrogen; the resulting analogue manifests mainly antiplasmodial rather than coccidiostatic activity. That the nitration of the aniline (**24-1**) perhaps surprisingly proceeds at the position *meta* to the amino group can be rationalized by the fact that the electron density will be higher *para* to the alkyl group than *para* to the protonated aniline (**24-2**). Catalytic reduction of the newly introduced nitro group leads to the diamine (**24-3**). This compound affords **amquinate** (**24-4**), when subjected to the quinoline-forming reaction sequence [28].
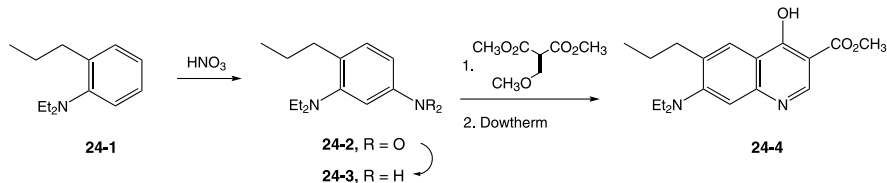
Antimalarial activity also predominates in a quinoline that bears a diaminoalkyl side chain at a rather different position from the agents noted in the previous section. Thus, Mannich condensation of the hydroxyquinoline (**25-1**) with formaldehyde and *N*,*N*-diethylpropylenediamine affords **clamoxyquin** (**25-2**) [29].
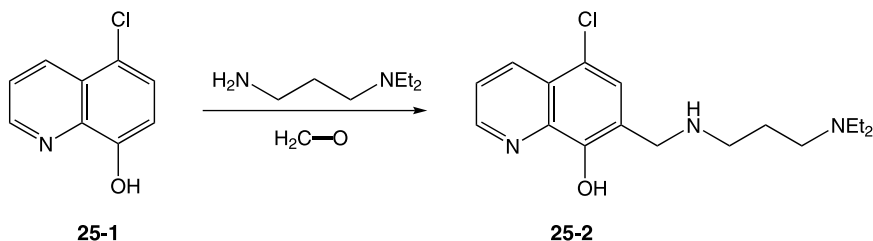
The quinoline nucleus sometimes serves as a surrogate for aromatic moieties; this is illustrated by two NSAIDs that are closely related to the anthranilic acid "fenac"

compounds discussed in Chapter 2. These two examples date from before the discovery of the role of prostaglandins in inflammation and effects on gastric mucosa. The glyceryl esters in these examples were probably included to avoid irritation of the stomach, thought at that time to be caused by exposure to the acidic carboxyl groups; serum esterases would quickly cleave these groups once the drug was absorbed. The first of these compounds, **glafenine** (**26-2**), is prepared by displacement of chlorine in chloroquine intermediate (**17-6**) by the amino nitrogen in glyceryl anthranilate (**26-1**) [30].
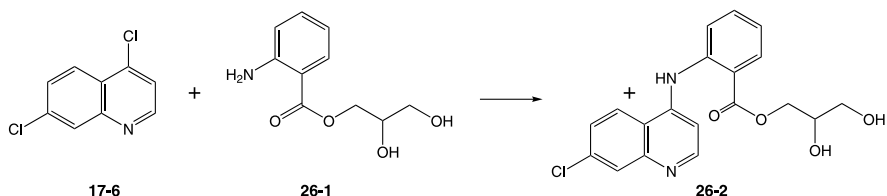
A somewhat different approach is used for the preparation of the analogue that contains a trifluoromethyl group. The scheme involves first the conversion of *ortho*-trifluoromethyl aniline (**27-1**) to a quinolol. The compound is thus condensed with EMME and cyclized thermally (**27-2**). That intermediate is then saponified; the resulting acid is decarboxylated and finally converted to the 4-chloroquinoline (**27-3**) by reaction with phosphorus oxychloride. The displacement of chlorine with methyl anthranilate (**27-4**) then affords the coupled intermediate (**27-5**). An ester interchange of that product with glycerol leads to the glyceryl ester. There is thus obtained the NSAID **flocatfenine** (**27-6**) [31].
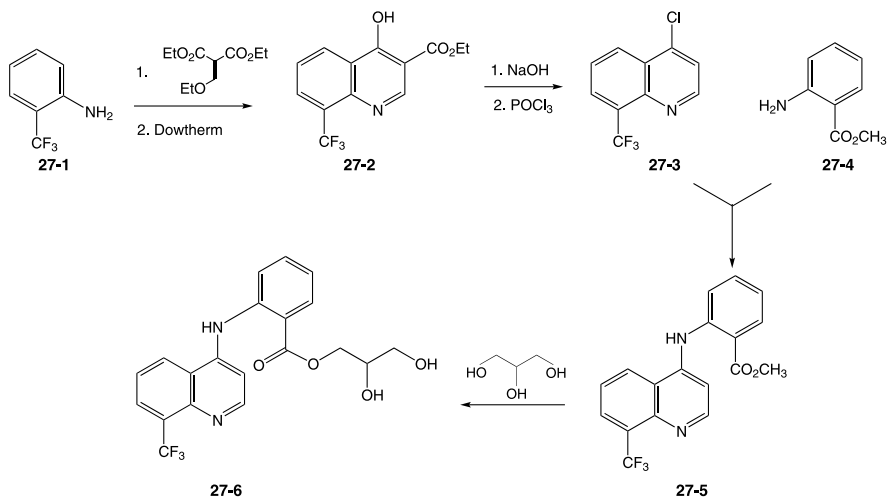
Similar considerations apply to leukotriene antagonists; quinoline rings provide a role comparable to the benzopyran in the antagonist **ablukast** (**11-7**), discussed earlier in this chapter. Reaction of the product (**28-1**) from side chain chlorination

of 2-methylquinoline with the phenoxide from 3-nitrophenol (**28-2**) leads to the corresponding ether (**28-3**). The nitro group is then reduced, for example, by catalytic hydrogenation to give the aniline (**28-4**). Acylation of the amino group with trifluro-methylsulfonyl chloride (triflyl chloride) gives the sulfonamide derivative, **ritolukast** (**28-5**) [32]; the acidity of the sulfonamide proton in this compound is comparable to that of carboxylic acids found in most leukotrienes antagonists.
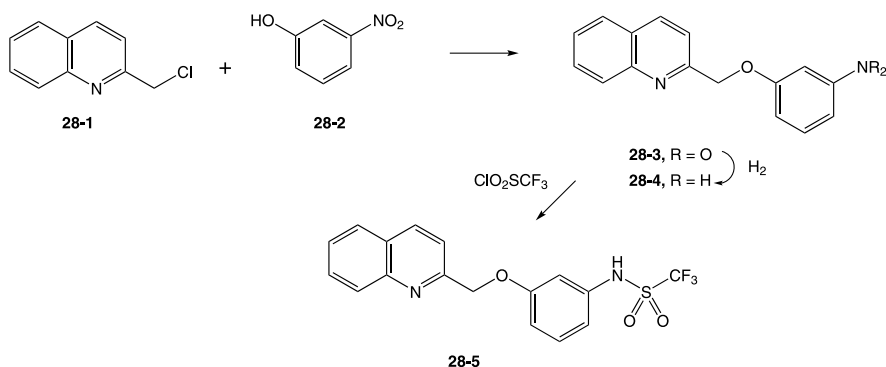
Preparation of a somewhat more complex leukotriene antagonist begins by aldol condensation of the methyl carbanion from quinoline (**29-1**) with *meta*-phthalalde-hyde (**29-2**) to give the stilbene-like derivative (**29-3**); dimer formation is presumably inhibited by the use of excess aldehyde. Reaction of that product with N,N-dimethyl-3-mercaptopropionamide in the presence of hexa-methylsilazane affords the silyl ether (**29-4**) of the hemimercaptal. Treatment of that intermediate with ethyl 3-mercaptopropionate leads to the replacement of the silyl ether by sulfur and the formation of the corresponding thioacetal (**29-5**). Saponification of the ester group leads to the carboxylic acid and thus to **verlukast** (**29-6**) [33].
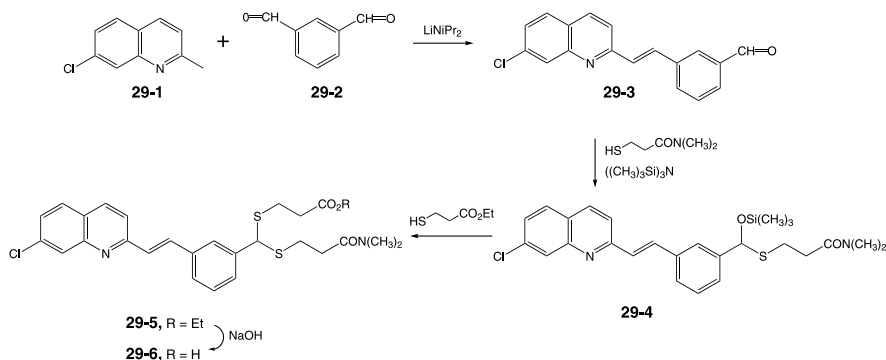
The synthesis of a much more complex leukotriene antagonist starts with the intermediate (**29-3**) from the preceding synthesis. The aldehyde is extended by two-carbon atoms by first reacting the carbonyl with methylmagnesium bromide.

The newly formed benzylic alcohol (**30-1**) is then oxidized with magnesium dioxide. Reaction of the resulting methyl ketone with methyl carbonate in the presence of a base adds the terminal carboxyl function. The anion from that intermediate with sodium hydride with the benzyl is then alkylated with the substituted benzyl chloride (**30-2**). Treatment of the first-obtained product with acid hydrolyzes both esters; the side chain acid then decarboxylates to yield (**30-3**). Reduction of the ketone with diborane in the presence of a chiral auxiliary affords the corresponding alcohol as a single eneatiomer; the acid is then re-esterified to yield (**30-4**). The final steps will involve discriminating between two hydroxyl groups. That in (**30-4**) is thus first covered as its silyl ether by reaction with phenyldimethylsiliyl chloride. Reaction of that product with methyl Grignard reagent adds two methyl groups to the ethyl ester. That resulting alcohol is then converted to its tetrahydropyranyl ether. The silyl group is removed with fluoride ion to yield (**30-5**). The newly revealed hydroxyl is then converted to a leaving group by reaction with mesyl chloride. Replacement of the mesyl group by sulfur on the intermediate (**30-6**) from a convergent scheme adds the last fragment. Removal of the tetrahydropyranyl group with a mild acid followed by saponification of the ester finally yeids **montelukast** (**30-8**) [34].
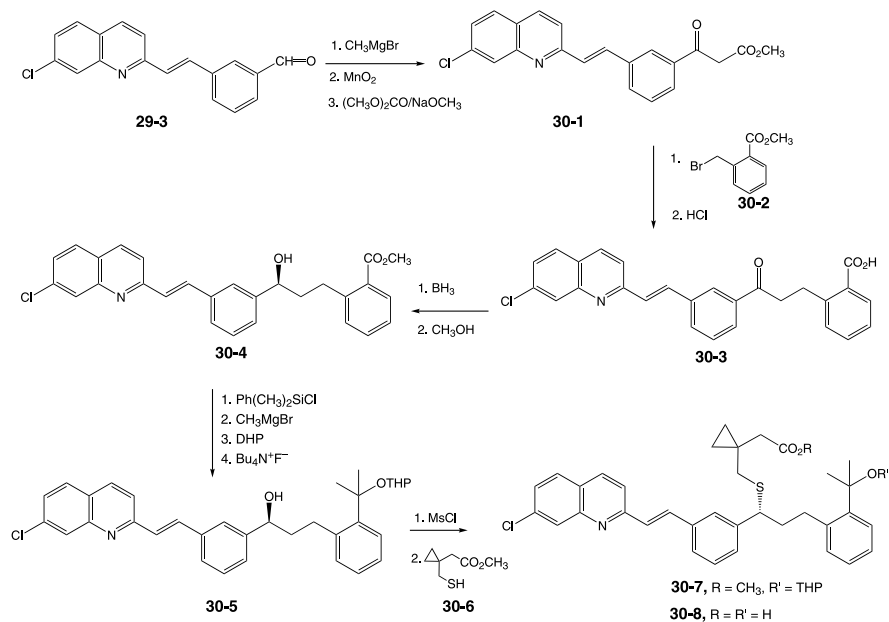
The quinoline-based tyrosine kinase inhibitor **pelitinib** (**31-11**) incorporates a Michael acceptor function in the side chain that can form a covalent bond with a nucleophile on the target enzyme. Such an interaction would result in the irreversible inhibition of the target kinase. Reaction of aniline (**31-1**) with DMF acetal leads to the addition of a carbon atom to aniline nitrogen in the form of an amidine (**31-2**). This intermediate is next reacted with nitric in acetic acid to form the nitrated

product (**31-3**). Condensation of that intermediate with ethyl cyanoacetate in the presence of acid affords the enamine (**31-4**) from the displacement of dimethylamine. Heating that product in Dowtherm then closes the ring via the ester group to form the cyano quinoline (**31-5**). Treatment of the enol (**31-5**) with phosphorus oxychloride thus affords the chlorinated derivative (**31-6**). Reaction of this last with 4-fluoro-3-chloroaniline (**31-7**) leads to the displacement of the ring chlorine by the basic nitrogen and thus the formation of (**31-8**). Treatment of that intermediate with iron powder in acetic acid serves to reduce the nitro group that was put in place early in the sequence to the amine (**31-9**). Acylation of that newly introduced amine with 4-*N*,*N*-dimethylaminobut-2-enoyl chloride (**31-10**) gives the irreversible kinase inhibitor pelitinib (**31-11**) [35].
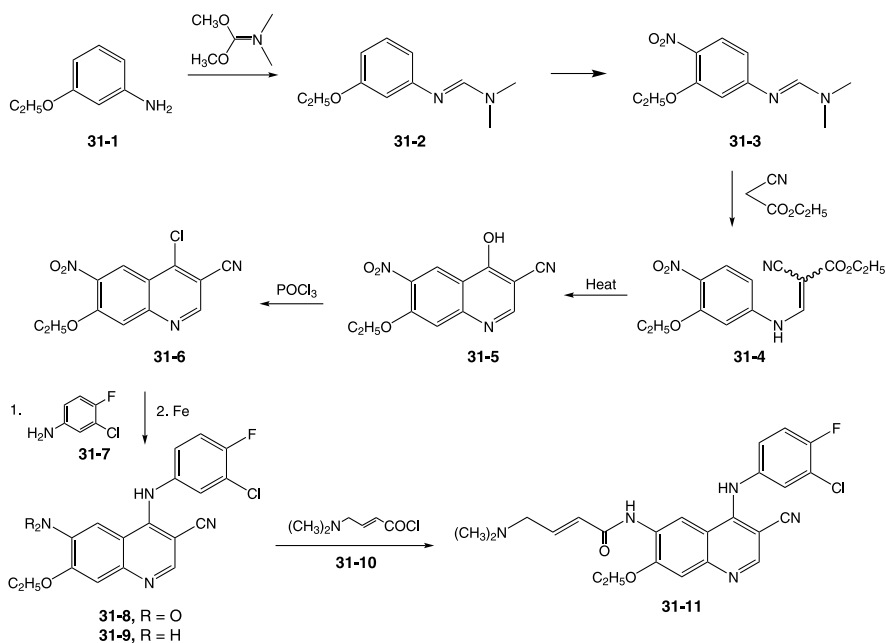
Neurokinins comprise a group of peptides involved in nerve transmission. Specific members of this class of mediators control such diverse functions as visceral regulation and CNS function. The nonpeptide neurokinin antagonist **talnetant** (**32-6**), for example, has been evaluated for its effect on irritable bowel syndrome and urinary incontinence as well as depression and schizophrenia [36]. The quinoline portion of this compound is prepared by base-catalyzed Pfitzinger condensation of isatin (**32-1**) with the methoxy acetophenone (**32-2**). The methoxy ether in the product (**32-3**) is next cleaved by means of hydrogen bromide (**32-4**). Amide formation with the chiral α-phenylpropylamine (**32-5**) affords the neurokinin antagonist talnetant (**32-6**) [37].
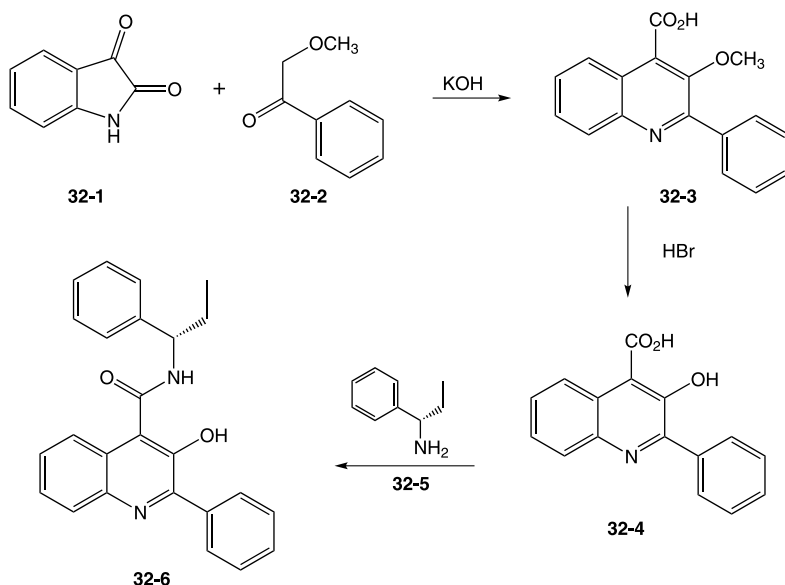
Schistosomes are yet another of the helminths that parasitize man. Infection is most often caused by entry through breaks in the skin during immersion in infected water. The very debilitating disease schistosomiasis is quite prevalent in the Third World and is often associated with irrigation schemes. The structure of one of the more effective antischistosomal drugs includes a partly reduced quinoline. The synthesis starts by chlorination of the methyl group on the heterocyclic ring in the dimethylquinoline (**33-1**); the displacement of chlorine with *iso*propylamine then gives the intermediate (**33-2**). High-pressure catalytic hydrogenation leads to selective reduction of the heterocyclic ring and the formation of the tetrahydro derivative (**33-3**). Nitration under standard conditions proceeds at the more electrophilic of the open positions on the aromatic ring to afford (**33-4**) [38]. This product shows reasonable antischistosomal activity in its own right and was probably at one time considered for clinical development. Pharmacokinetic experiments showed that the metabolite
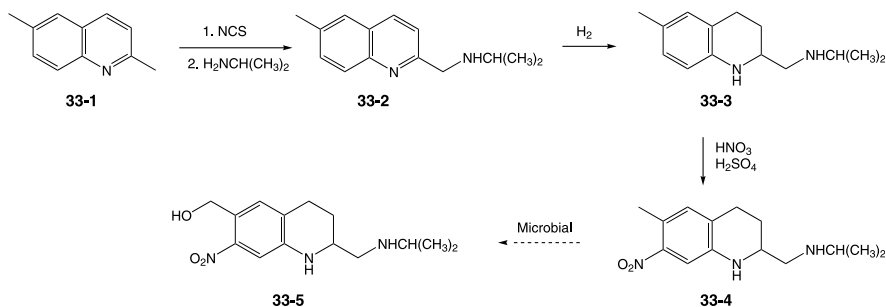
from the hydroxylation of the methyl group had superior activity to the parent drug. Microbiological experiments revealed that the mold *Aspergillus sclerotiorum* affects the same oxidation. Thus, fermentation of the methyl compound (**33-4**) with that organism results in the introduction of the hydroxyl group and the formation of **oxamniquine** (**33-5**).

Dietary cholesterol needs be esterified in order to be absorbed from the gut. The enzyme, cholesteryl ester transfer protein (CETP), then completes the absorption of cholesterol. Drugs that interfere with the action of these peptides would aid in lowering cholesterol levels by complementing the action of the statins that inhibit the endogenous production of cholesterol. The CEPT inhibitor torcetrapib (**34-9**) proved very effective in lowering cholesterol levels in humans; the drug not only lowered low-density lipoproteins (LDL and VLDL) but also raised levels of high-density, "good" lipoproteins (HDL). This agent, which had only a brief time on the market due to adverse safety reports, is included here to illustrate an unusual method for preparing tetrahydroquinolines. Reaction of the trifluoromethylaniline (**34-1**) with propanal in the presence of benzotriazole (**34-2**) affords the aminal (**34-3**). Condensation of (**34-3**) with the vinyl carbamate (**34-4**) adds three carbon atoms in what may be viewed formally as a 2+3 cycloaddition sequence. This yields the tetrahydroquinoline ring (**34-5**) with expulsion of the benzotriazole fragment. The ring nitrogen is then protected as its ethyl carbamate by acylation with ethyl chloroformate (**34-6**). The benzyl carbamate function on nitrogen at the 4 position is next removed by reduction with ammonium formate over palladium to afford the primary amine; this compound is then resolved as its dibenzyl tartrate salt to afford the 2*R*,4*S* isomer (**34-7**). Reductive amination with the *bis*-trifuoromethyl benzaldehyde (**34-8**) in the presence of sodium triacetoxy borohydride followed by acylation with methyl chloroformate completes the synthesis of **torcetrapib** (**34-9**) [39].
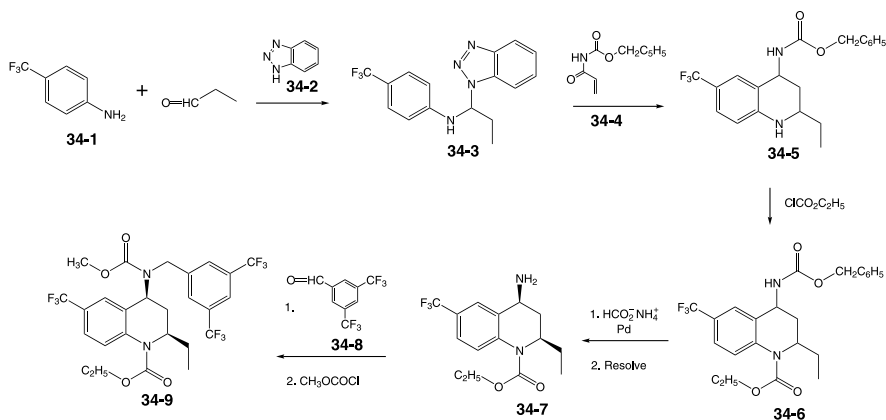
A tetrahydroquinoline moiety provides the nucleus for yet another anticholinergic agent intended as a drug for treating urinary incontinence. The classic Pictet-Spengler provides the method for building a dihydroisoquinoline ring for one of these agents.

Thus, treatment of the benzamide (**35-1**) from 2-phenethylamine with phosphorus oxychloride probably results in an initial formation of a transient enol chloride; this then cyclizes to (**35-2**) under reaction conditions. The imine is then reduced with sodium borohydride. Resolution by means of the tartrate salt affords (**35-3**) in optically pure form. Acylation of that intermediate with ethyl chloroformate leads to carbamate (**35-4**). Reaction of this last with the anion from chiral quiniclidol (**35-5**) interestingly results in the equivalent of an ester interchange. There is thus obtained the anticholinergic agent **solifenacin** (**35-6**) [40].
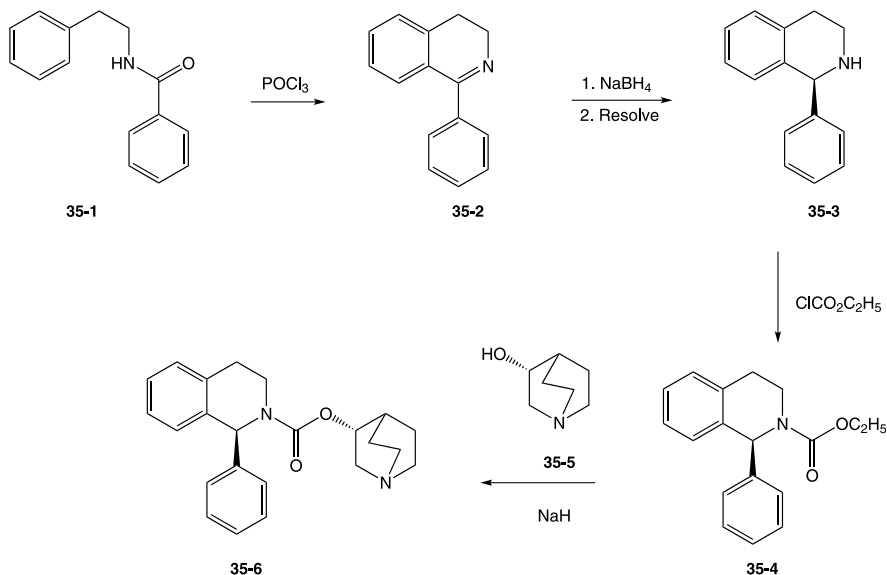
An important step in cell proliferation involves the addition of the terpene, farnesol, to cysteine residues near the end of the protein chains. Inhibitors of the enzyme that catalyzes this step, farnesyl transferase, provide yet one more mechanism for interrupting the multiplication of malignant cells. Acylation of N-methylaniline (**36-2**) with the cinnamoyl chloride (**36-1**) comprises the first step in the synthesis of the inhibitor, **tipifarnib** (**36-8**). Treatment of the resulting amide (**36-3**) with polyphosphoric acid leads to an attack of the protonated olefin onto the adjacent benzene ring with the formation of the tetrahydroquinolone (**36-4**). This intermediate is then reacted with 4-chlorobenzoyl chloride (**36-5**) in the presence of a Friedel–Crafts catalyst to afford the corresponding ketone. The heterocyclic ring is next dehydrogenated by reaction with bromine. The initially formed quaternary bromide apparently loses hydrogen bromide under reaction conditions to give the unsaturated quinolone (**36-6**). Treatment of this last compound with the anion obtained from N-methylimidazole and butyl lithium leads to the addition of that heterocycle to the ketone. The thus-formed carbinol (**36-7**) is then treated with ammonia. The quaternary carbinol then in essence solvolyses so as to replace the hydroxyl group by a primary amine forming tipifarnib (**36-8**) [41,42].
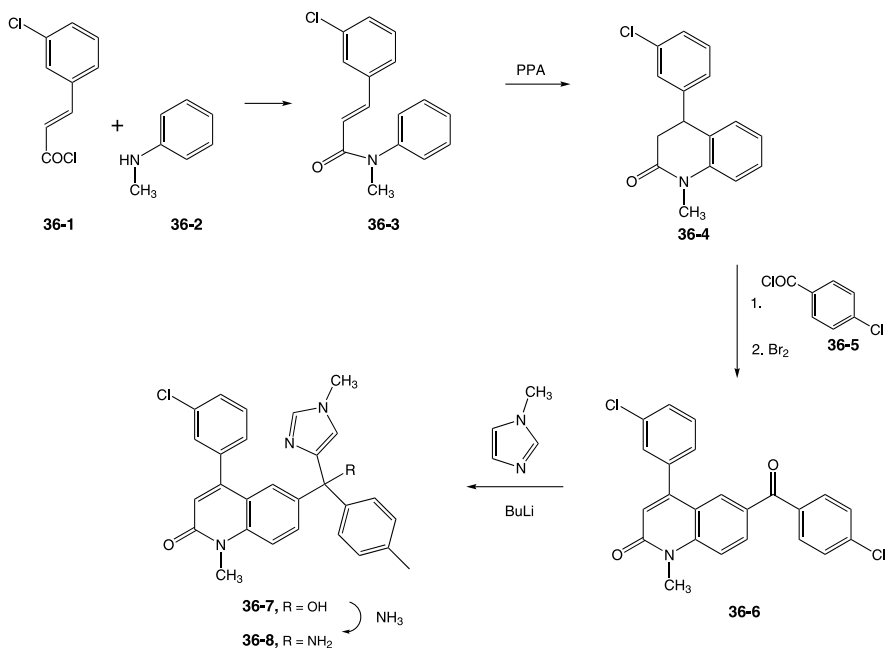
A roundabout route is used to prepare tetrahydroquinolines with reduced carbocyclic rings since direct reduction, as noted above, adds hydrogen to the hetero-cyclic ring. The key reaction in this scheme involves a variant of the Hantzsch pyridine synthesis. Condensation of the imine (**37-1**) from dihydroresorcinol with ethoxymethylenepropionaldehyde (**37-2**) can be envisaged as proceeding through
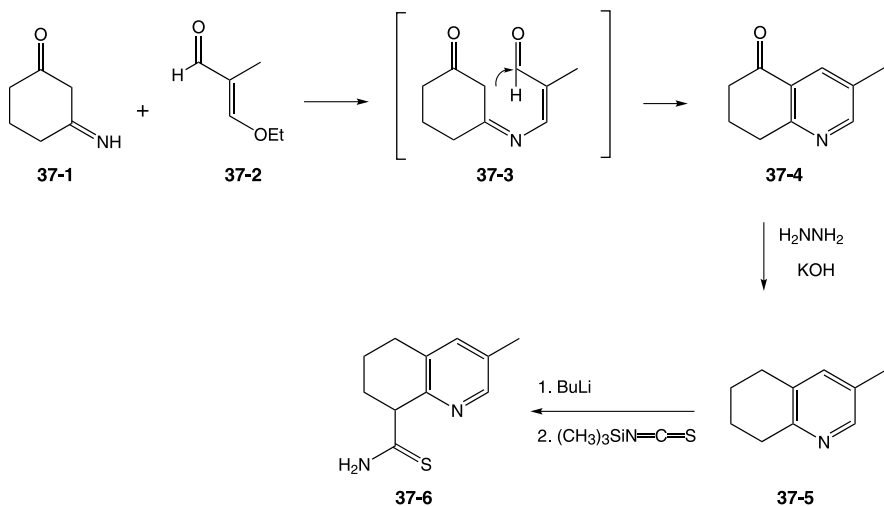
the addition-elimination product (**37-3**). Aldol condensation will then result in ring closure and, after bond reorganization, the formation of the fused pyridine (**37-4**). The carbonyl group in that product is then removed by Wolff-Kischner reaction with hydrazine and potassium hydroxide to give (**37-5**). Reaction of that compound with butyl lithium proceeds preferentially at the 8 position, where the metalated center can be stabilized by the adjacent ring nitrogen. Addition of the carbanion to trimethylsilylisothiocyanate leads to the formation of a thioamide function. There is thus obtained **tiquinamide** (**37-6**) [43]. The antiulcer activity displayed by this compound was attributable largely to its anticholinergic activity mechanism. Antacids that act by this mechanism have been abandoned with the advent of the very specific histamine H_2 blockers and sodium-potassium pump inhibitors.

11.1.5. Quinolones

11.1.5.1. Antibacterial Agents. The antibiotics that have led to the major advances in the treatment of infectious disease all depend on selective toxicity to microorganisms. Examples that have already been discussed include the inhibition of PABA by sulfonamides and folates by DHFR inhibitors. The antagonism of bacterial cell wall synthesis by β-lactams is detailed in Chapter 14. The quinolone antibiotics act directly on DNA-mediated microbial replication. Rearrangement of sections of supercoiled DNA to permit transcription is a necessary first step in that process. A set of enzymes known as topoisomerases control the topology of this process in both bacteria and higher organisms. The enzyme in essence maintains the integrity of the DNA chain even in the presence of the temporary cuts required for uncoiling. The quinolones, it has been found, specifically interact with a subclass of topoisomerases, known as gyrases, that are crucial for bacterial replication.

The lead compound for this series, **nalidixic acid** (**38-6**), which is actually a naphthyridine rather than a quinolone, was first introduced over four decades ago. That compound for many years found its niche as a rather effective drug for the treatment of urinary tract infection. The rediscovery of the general structural class in the early 1980s hinged on the discovery of the importance of fluorine at the 6 position and basic nitrogen at position 7. This renewed research led to the development of a very large series of potent broad spectrum antibiotics. This is reflected in the fact that more than 20 quinolone antibiotics have been granted U.S. nonproprietary names.

The chemistry used to prepare the antischistosomal hydroxyquinolines provided the initial entry to this series. Thus, addition-elimination of aminopicoline (**38-1**) to EMME (**38-2**) gives the corresponding enamino ester (**38-3**). Thermal cyclization of that intermediate leads to the hydroxyquinoline (**38-4**). Reaction of the ambient anion from that compound leads to alkylation via the keto tautomer and thus the formation of the *N*-alkylated derivative (**38-5**). Saponification of the ester then gives **nalidixic acid** (**38-6**) [44]. It has incidentally been shown that the presence of the strong Michael acceptor function in this series plays a little role in the mechanism of action in these compounds.

The same scheme affords a true quinolone when applied to an aniline. Condensation of piperonylamine (**38-7**) with EMME followed by cyclization of

the intermediate gives the quinolinol (**38-8**). Alkylation as above followed by saponification affords the antibiotic **oxolinic acid** (**38-10**) [45].
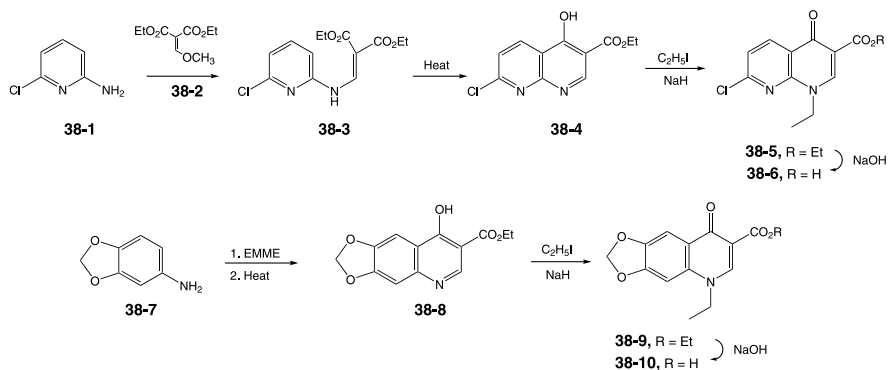
One of the earlier second-generation quinolones indeed includes fluorine at the 6 position and a basic function at the 7 position, characteristic of the more potent drugs that also feature a broader spectrum of antibacterial activity. The starting material (**39-3**) for one of these agents is prepared by application of the same scheme as above to the substituted aniline (**39-1**). Nucleophilic aromatic displacement with *N*-methylpiperazine (**39-4**) proceeds at the 7 position due to activation by the carbonyl group *para* to the chlorine (**39-5**). Saponification of the displacement product leads to **pefloxacin** (**39-6**) [46].
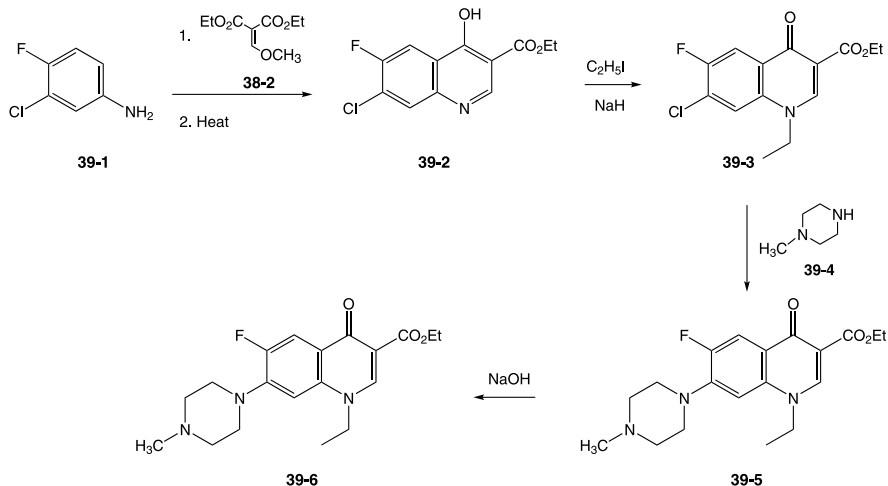
Very much the same strategy is used to synthesize a quinolone that contains an additional fused ring. This agent features a broad-spectrum antibacterial activity in spite of the lack of a nitrogen substituent at position 7. It is of note in this case

that the use of a secondary amine leads directly to a quinolone, doing away with the need for the alkylation step. The tricyclic system is obtained directly by condensation of the tetrahydroquinoline (**40-1**) with EMME followed by thermal cyclization (**40-2**). Saponification of that intermediate then affords **ibafloxacin** (**40-3**) [47].
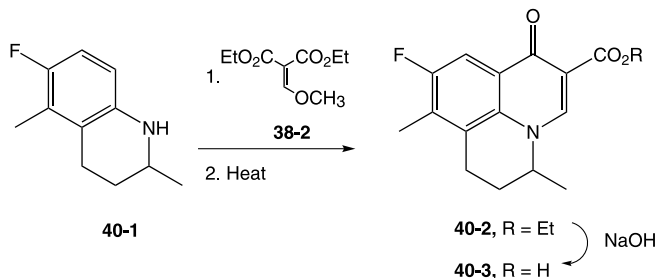
The hydroxyquinoline (**39-2**) provides the starting material for a quinolone that incorporates a hydrazine function. Reaction of (**39-2**) with 2,4-dintrophenyl *O*-hydroxylamine ether (**41-1**) in the presence of potassium carbonate leads to a scission of the weak N-O hydroxylamine bond by the transient anion from the quinolone; the excellent leaving character of 2,4-dinitrophenoxide adds the driving force for the overall reaction, resulting in alkylation on nitrogen to form the hydrazine (**41-2**). The primary amine is then converted to the formamide (**41-3**) by reaction with the mixed acetic-formic anhydride. Alkylation of that intermediate with methyl iodide followed by removal of the formamide affords the monomethylated derivative (**41-4**). Chlorine at the 7 position is then displaced by *N*-methylpiperazine and the product saponified. There is thus obtained **amifloxacin** (**41-6**) [48].
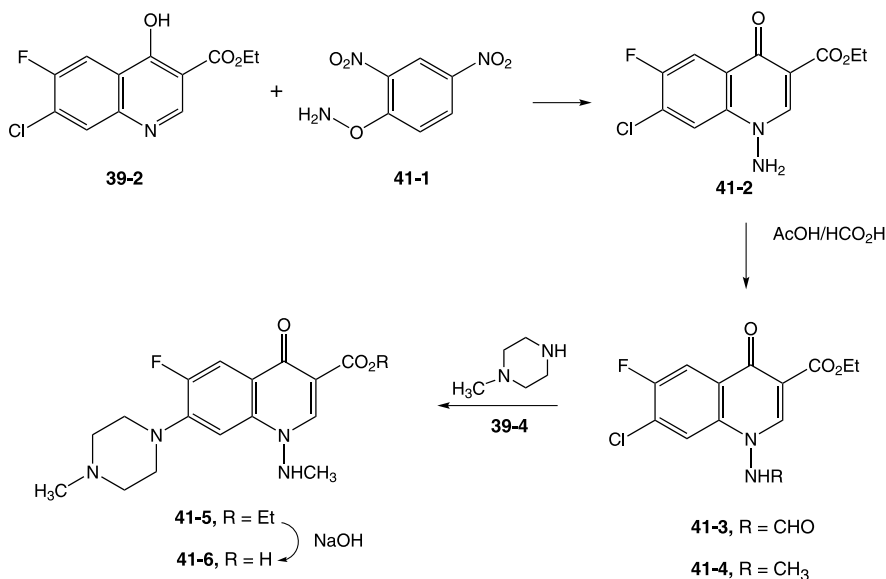
One alternate approach to the construction of the quinolone nucleus relies on forming the heterocyclic ring by an internal aromatic nucleophilic displacement reaction. The requisite ketoester (**42-2**) can be obtained by base catalyzed acylation of the methyl group on acetophenone (**42-1**) with methyl carbonate; an alternate procedure for this transform, used to prepare (**43-1**) below, involves ethyl magnesium carbonate as the reagent. Condensation of the product with methyl orthoformate in the presence of acetic anhydride then gives the methoxymethylene derivative (**42-3**). Addition-elimination with *para*-fluoroaniline (**42-4**) replaces the methoxyl group by the aromatic amine to give (**42-5**). The anion on nitrogen obtained on treatment of that intermediate with a base displaces the nitrogen on the adjacent ring to form the pyridone ring, yielding quinolone (**42-6**). Displacement of the remaining chlorine with N-methylpiperazine followed by saponification then affords **difloxacin (42-8)** [49].
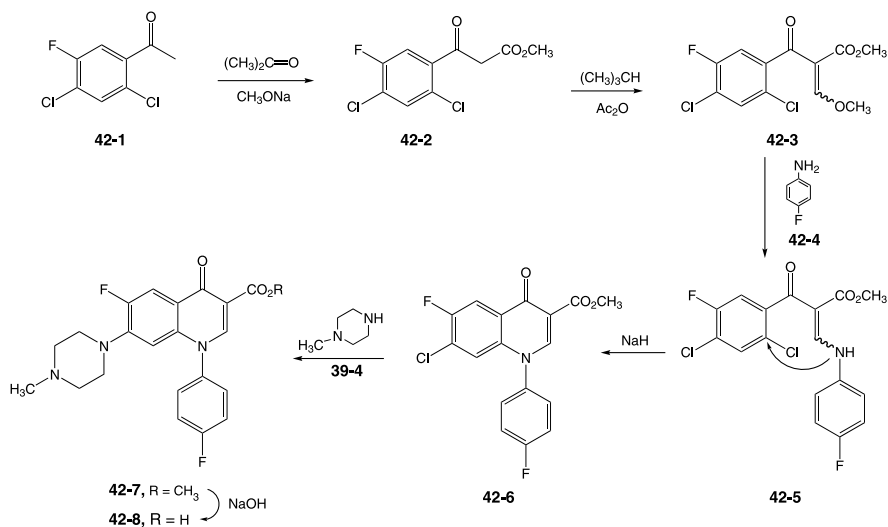
This approach seems to offer considerable flexibility in that the piperazine moiety can be incorporated at an early stage. Treatment of the tetrafluorobenzoyl acetate (**43-1**) with N-methylpiperazine results in the displacement by nitrogen of the more activated fluorine at the 4 position to form (**43-2**). Condensation of this intermediate with dimethylformamide acetal leads to the formation of the eneamide derivative (**43-3**). Reaction of that with 2-methylethanolamine (alaninol) leads to an amine exchange and the formation of the intermediate (**43-4**). This cyclizes to the quinolone (**43-5**) on reaction with potassium fluoride in DMF, a combination that often acts as a strong base. Treatment of this product with sodium hydride leads to the corresponding alkoxide; this displaces the adjacent fluorine in spite of its lack of activation to form the oxygen containing ring (**43-6**). The same intermediate can be obtained directly from (**43-4**) by reaction with potassium fluoride under more strenuous conditions. Saponification of the ester group completes the synthesis of **ofloxacin** (**43-7**) [50].
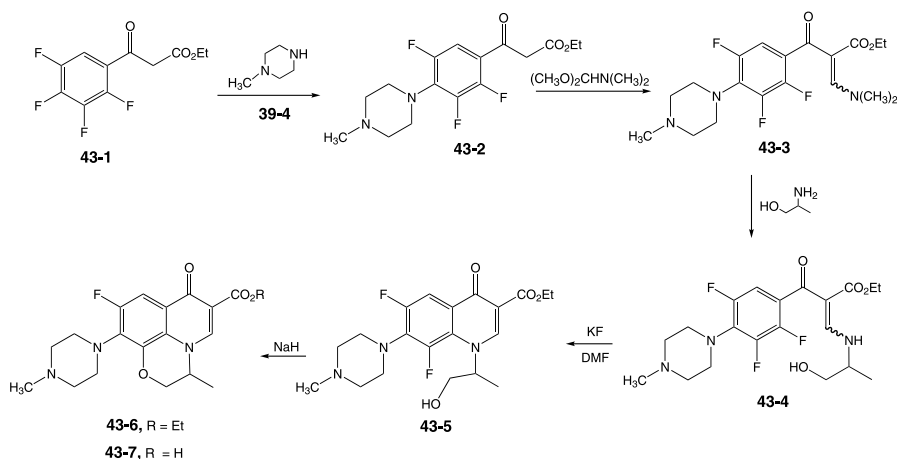
A variation on that theme involves the construction of the eneamide intermediate by direct acylation on carbon of an enamine, as illustrated in the synthesis of the *N*-methyl analogue (**44-6**) of the widely used quinolone **ciprofloxacin** (**44-7**). Condensation of the cyclopropyl enamine (**44-2**) from ethyl formylacetate with the benzoyl chloride (**44-1**) in the presence of triethylamine gives the acylation product (**44-3**). Reaction of the product with a strong base leads the resulting nitrogen anion to displace chlorine on the benzene ring and thus form the quinolone (**44-4**). Incorporation of the *N*-ethylpiperazine function followed by saponification of the product leads to **enrofloxacin** (**44-7**) [51].
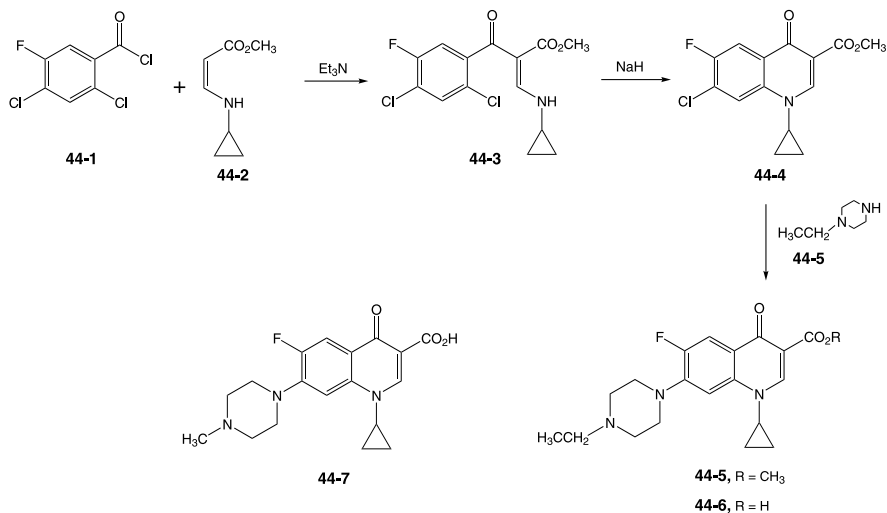
The preparation of quinolones bearing a substituent at position 5 is complicated by the greater electrophilic character of the 8 position. One scheme for resolving the problem consists in blocking access to position 8 by first adding a readily removable

group to that center. The scheme starts with the conversion of the carboxylic acid in (**45-1**) to its dimethyloxazoline derivative (**45-3**) by reaction with the dimethyl ethanolamine (**45-2**). Lithium disopropylamide (LDA) then removes a proton from the 8 position; treatment of that anion with trimethylsilyl iodide leads to the silylated intermediate (**45-4**). A second round of LDA then generates a carbaninon at the only open position; reaction with methyl iodide leads to the corresponding 5 methyl derivative (**45-5**). Treatment of that product with cesium fluoride breaks the carbon–silicon bond, removing the silyl group; aqueous acid then hydrolyzes the oxazoline to afford the free acid (**45-6**). This last intermediate is then taken on to the quinolone (**45-9**) [52] by essentially the same scheme as that used to prepare difloxacin (**42-7**), with the difference that the carboxyl in (**45-6**) is extended to the ketoacetate (**45-7**) by means of ethyl magnesiumacetate. Treatment of (**45-9**) with 2-methylpiperazine proceeds by reaction at the less hindered of the two amino groups to yield (**45-8**), soponification the affords **grepafloxacin (45-10)** [53].
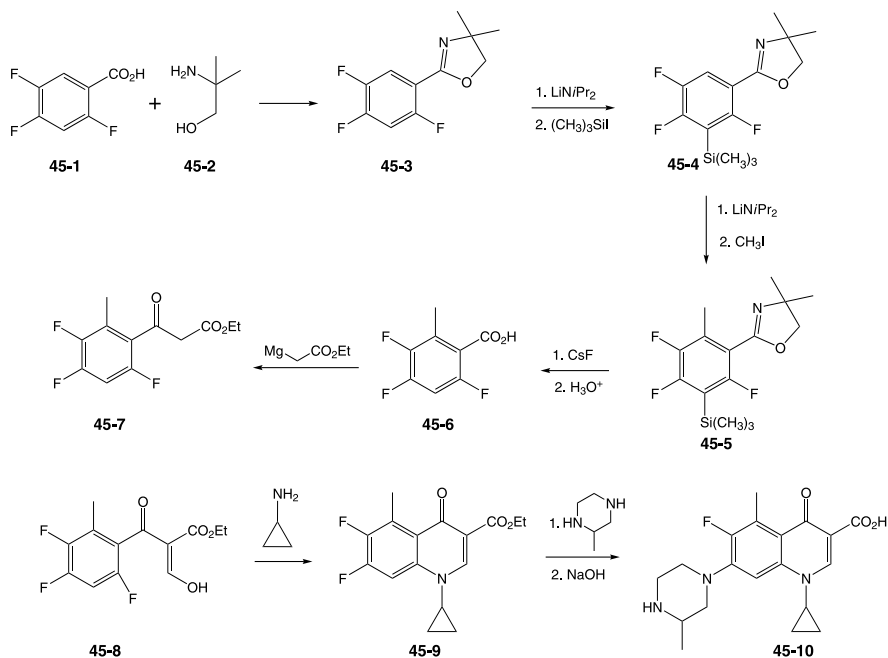
The dibasic side chain at position 7 can be alternatively provided by a substituted amino alkyl pyrrolidine. Preparation of that diamine in chiral form starts with the extension of the ester function in pyrrolidone (**46-1**) by aldol condensation with ethyl acetate (**46-2**). Acid hydrolysis of the β-ketoester leads to the free acid that then decarboxylates to form an acetyl group (**46-3**). The carbonyl group is next converted to an amine by sequential reaction with hydroxylamine to form the oxime, followed by catalytic hydrogenation. The desired isomer (**46-4**) is then separated

from the resulting mixture of diastereomers. Reaction with *tert*-butoxycarbonyl chloride leads to the urethane (**46-5**). Treatment of that intermediate with lithium aluminum hydride results in a reduction of the ring carbonyl as well as that on the side chain to yield the diamine (**46-6**). Removal of the phenethyl protecting group by hydrogenation over palladium completes the synthesis of the side chain diamine (**46-7**) [54]. In a convergent scheme, the substituted aniline (**46-8**) is taken on to quinolone (**46-9**) by a sequence that starts by condensation with EMME followed by thermal cyclization of the enamide [55]. Reaction of the quinolone with the diamine (**46-7**) results in the aromatic neucleophilic displacement of the fluorine group at position 7 (**46-9**). Saponification of the ester (**46-10**) then leads to the antibacterial agent **premafloxacin** (**46-11**) [56].
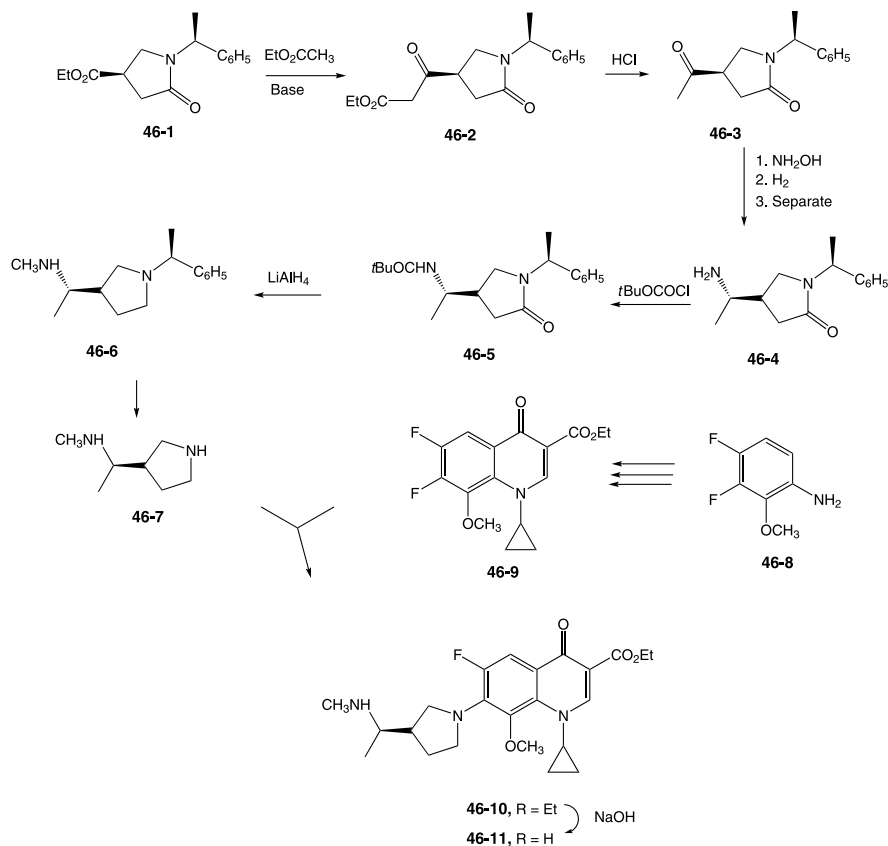
Replacing one of the protons on the cyclopropyl group by fluorine introduces an element of asymmetry into that moiety. A significant portion of the synthesis of **sitafloxacin** is consequently devoted to the preparation of that substituent in chiral form. Reaction of the chiral auxiliary aminoalcohol (**47-1**) with phosgene closes the ring to afford the oxazolidone (**47-2**). This is then treated with the methyl acetal from acetaldehyde; the ring amide nitrogen displaces one of the methoxy groups to give the corresponding carbinolamine derivative (**47-3**). Heating this intermediate leads to a loss of methanol to give the vinyl amine (**47-4**). The addition of

fluoromethylene carbene, generated from fluoromethyl iodide and diethyl zinc, leads to the formation of the cyclopropyl group (**47-5**). The steering influence of the proximate chiral auxiliary leads to the formation of the *cis*-isomer as a single enantiomer. Catalytic hydrogenation leads to a scission of the benzyl–nitrogen and benzyl–oxygen bonds; the transient carbonate disintegrates on workup to afford chiral *cis*-amine (**47-6**). The rest of scheme then follows the traditional route for forming quinolones. Thus, reaction of (**47-6**) with the ethoxymethylene intermediate (**47-7**) leads the amine to replace the ethoxy group to afford (**47-8**). The cylization to a quinolone (**47-9**) in this case is affected with sodium hydride. Treatment of this intermediate with the spiro diamine (**47-10**) leads to the displacement of fluorine and the formation of the alkylation product (**47-11**). Deprotection by acid catalyzed cleavage of the *ter*-butoxycarbonyl group followed by saponification then yields the quinolone antibacterial agent **sitafloxacin** (**47-12**) [57].
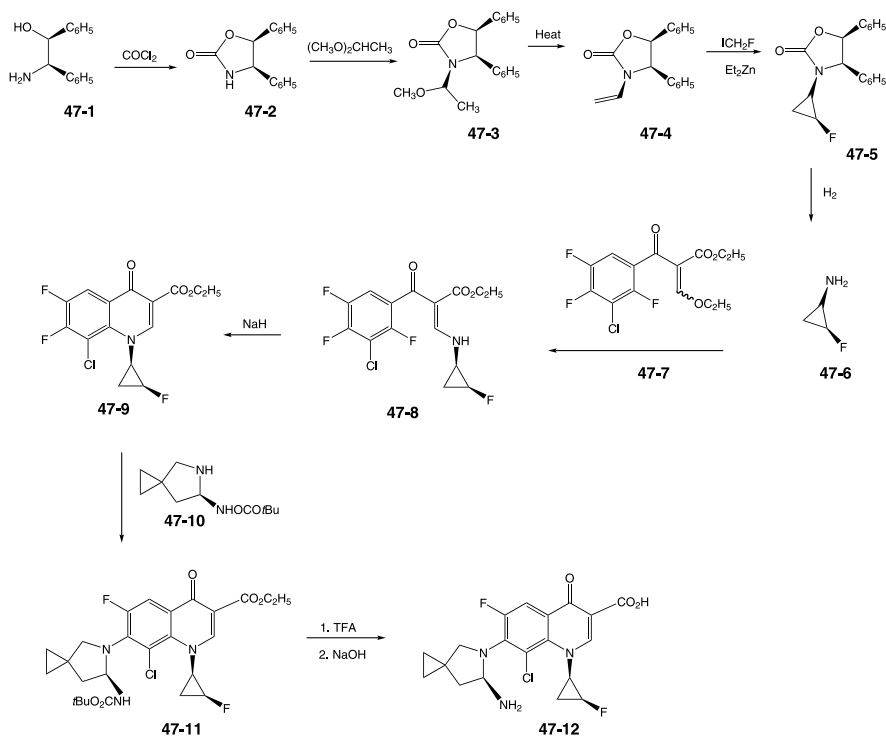
A good antibacterial is retained when an aromatic ring is interposed between the quinolone ring and the distant basic center at position 9. The palladium catalyzed aromatic cross-coupling reaction plays a central role in the preparation of the quinolone **garenoxacin** (**48-4**). The starting quinolone (**48-2**) is again prepared by one of the standard schemes. Suzuki cross-coupling of the bromine atom in (**48-2**) with the boronic acid from dihydroisoindole (**48-1**) leads to the coupling product (**48-3**). The trityl protecting group on isoindole nitrogen is then removed by treatment with acid. Saponification of the ester then yields the antibacteria quinolone **garenoxacin** (**48-4**) [58].

48-1   **48-2**   **48-3**, R = C(C$_6$H$_5$)$_3$, R' = Et
48-4, R = R' = H

11.1.5.2. Miscellaneous Quinolones.
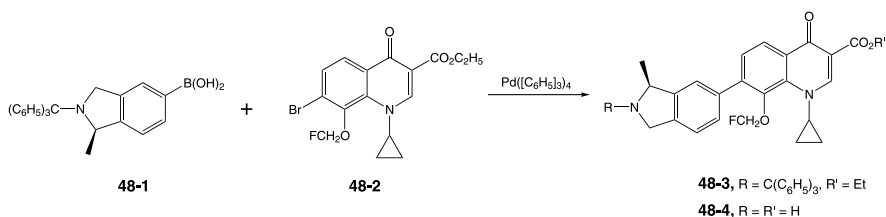
11.1.5.2. Miscellaneous Quinolones. Both methods for forming the hetero-cyclic ring in quinolones involved cyclization into the carbocyclic ring. A closely related quinolone that displays cardiovascular rather than antibiotic activity is con-structed by a condensation that closes the bond at the 2,3 position in the heterocyclic ring. The starting material (**49-2**) is obtained by reaction of the aminoacetophenone derivative (**49-1**) with ethyl formate. Heating the product in ethylene glycol methyl ether leads to an aldol-like cyclization and the formation of a quinolone ring. The product, **flosequinan** (**49-3**) [59], displays vasodilator and cardiotonic activities.

49-1   **49-2**   **49-3**
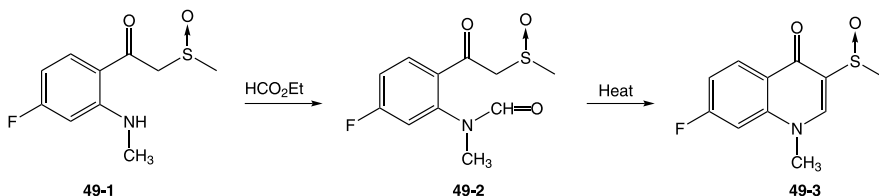
The product from the formal replacement of the benzimidazolone function in itasetron (**57-6**, Chapter 10) by a quinolone has been reported to display much the same serotonin antagonists activity of the former. In the absence of a specific reference to the synthesis, the starting quinolone is speculatively formed by reaction of cyclo-hexylaniline (**50-1**) with EMME to produce the enamide (**50-2**) from displacement

50-1   **50-2**   **50-3**   **50-4**

50-5
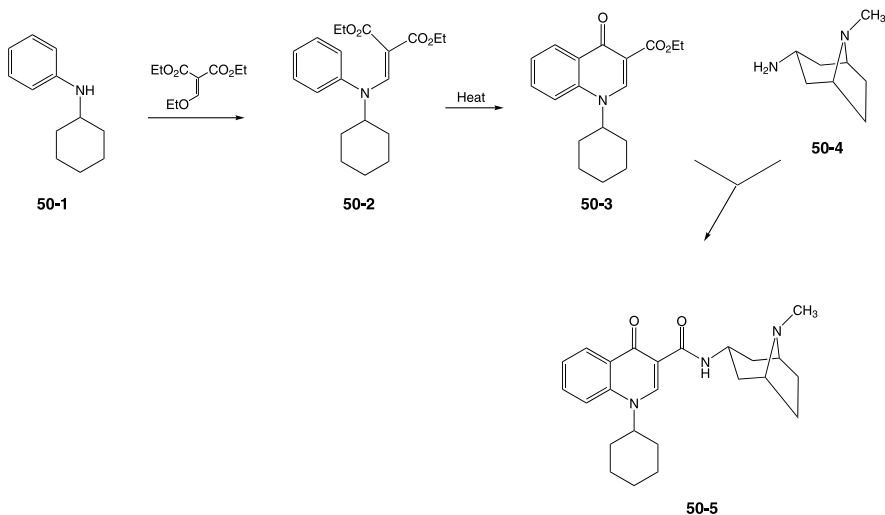
of the ethoxy group. Thermal cyclization would then afford the heterocycle (**50-3**). An amine-ester interchange of this last intermediate with the same bridged bicyclic diamine (**50-4**) as that used for itasetron would then afford **mirisetron** (**50-5**).

11.1.6. Isoquinoline and Its Derivatives

The ubiquity of the isoquinoline structure among natural products might lead to the expectation of a correspondingly large number of therapeutics that incorporate this nucleus. The relatively small number of isoquinolines that show useful biological activity is thus somewhat of a surprise. It should be added that the examples below are included more for illustration of the chemistry of this heterocyclic system than for their therapeutic importance, since most have long since passed out of use.

The best-known drug that incorporates the isoquinoline nucleus is **papaverine** (**51-5**). This venerable natural product, which accompanies the opioids in various *papaver* species, exhibits muscle-relaxing properties in various isolated muscle strip preparations. On the strength of this and some related data, the drug found some use in the past as a spasmolytic agent and as a vasodilator to improve cerebral blood circulation. The synthesis of this drug discussed below was first described by Pictet [60] and illustrates what is now known as the Pictet-Spengler reaction. The first step consists of a reaction of homoveratrylamine (**51-1**) with homoveratroyl chloride (**51-2**) to give the amide (**51-3**). Treatment of that intermediate with a strong Lewis acid as, for example, phosphorus oxychloride leads to cyclodehydration and the formation of the dihydroisoquinoline (**51-4**). Dehydrogenation of that product with palladium affords **papaverine** (**51-5**).
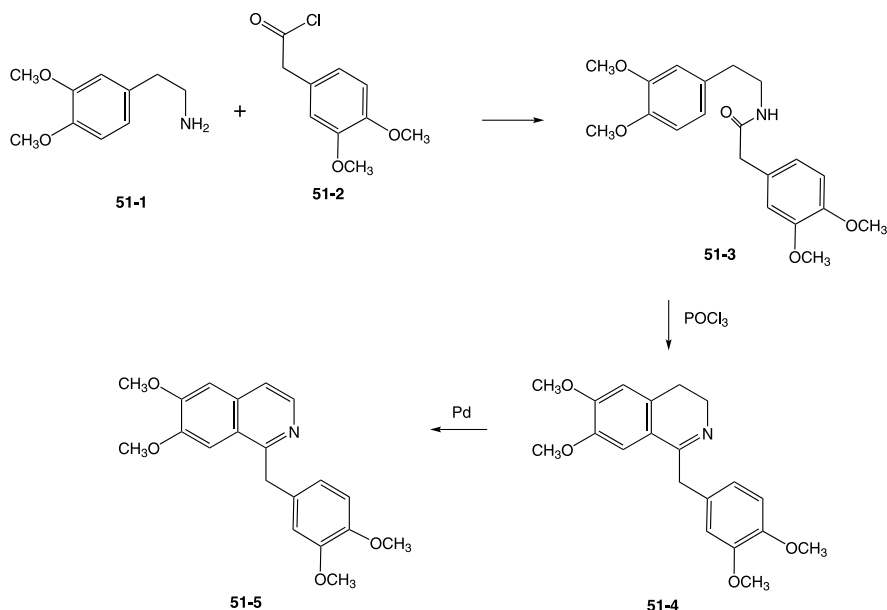
A dihydroisoquinoline was at one time investigated in some detail as an antiviral compound. Acylation of β-phenethylamine (**52-1**) with 2-(4-chlorophenoxy)acetyl

chloride (**52-2**) gives the corresponding amide (**52-3**). Cyclodehydration of that intermediate, this time using phosphorus pentoxide, gives **famotine** (**52-4**) [61].
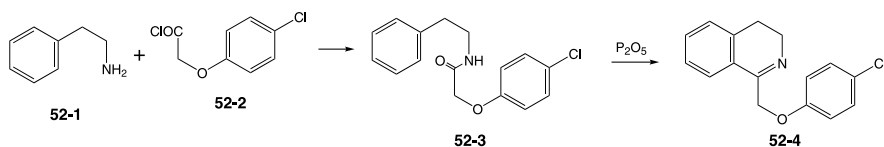
The Pictet-Spengler reaction provides the key intermediate in the preparation of a fused tricyclic compound, **tetrabenazine** (**53-6**), a compound that has been used as an antipsychotic agent and is still being studied as a treatment for some of the deleterious side effects of the antipsychotic dopamine antagonists. Reaction of the arylethylamine (**51-1**) with the half-acid chloride from methyl malonate gives the expected amide (**53-2**). This is then subjected to the cyclodehydration reaction and the product reduced to the tetrahydroisoquinoline (**53-3**) by catalytic hydrogenation. Treatment of that intermediate with diethyl isopropylmalonate and formaldehyde leads to a rather unusual Mannich reaction that results in the formation of the homologation-alkylation product (**53-4**). Hydrolysis of the ester followed by decarboxylation of the di-acid and then re-esterification gives the di-ester (**53-5**). Base-catalyzed Dieckmann cyclization leads to the formation of the carbethoxycyclohexanone ring. The remaining carbethoxyl group in the product is then removed by repeating the hydrolysis and decarboxylation sequence. There is thus finally obtained **tetrabenazine** (**53-6**) [62].
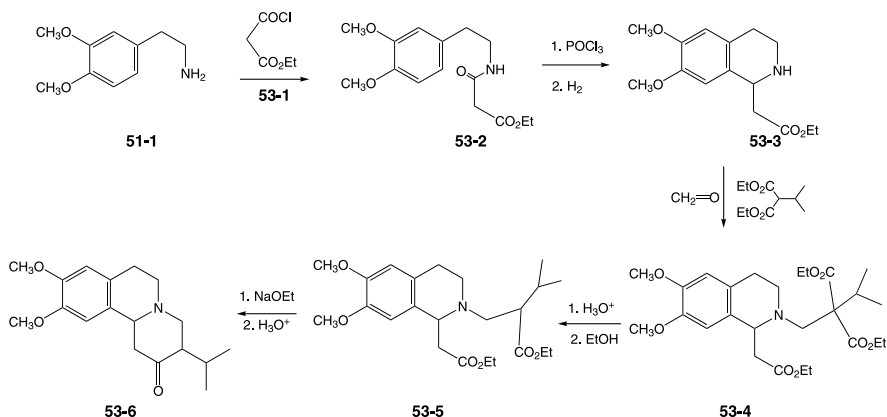
A concise synthesis of a tetrahydroisoquinoline is designed to take into account the fact that the benzaldehyde (**54-1**) is more readily available than the required homologue (**54-3**). Reaction of the former with ethyl chloroacetate and sodium hydride leads initially to simple the addition of the anion to the carbonyl group. The second step in this Darzens reaction comprises the internal displacement by the resulting alkoxide of the adjacent chlorine to afford the glycidic ester (**54-2**). Treatment of that with a base results in the formation of the corresponding sodium salt. This salt is then allowed to react with 3,4-dihydroxy-β-phenethylamine (**54-4**, dopamine) under Pictet–Spengler conditions. The strong acid present in the medium brings about as

the first step the decarboxylative rearrangement of the free acid form salt to the arylacetaldehyde (**54-3**). This aldehyde then adds to the amino group in dopamine to form a carbinolamine. Either species of the resulting Schiff base (**54-5**) then attacks the highly activated aromatic ring. This reaction, which amounts to a cyclodehydration, results in the formation of the isoquinoline (**54-6**). Catalytic reduction of the double bond then yields **trimethoquinol** (**54-7**) [63]. This is one of a small group of compounds devoid of an aminoalcohol moiety that act as β-adrenergic agonists; it has as a consequence been investigated as a bronchodilator.
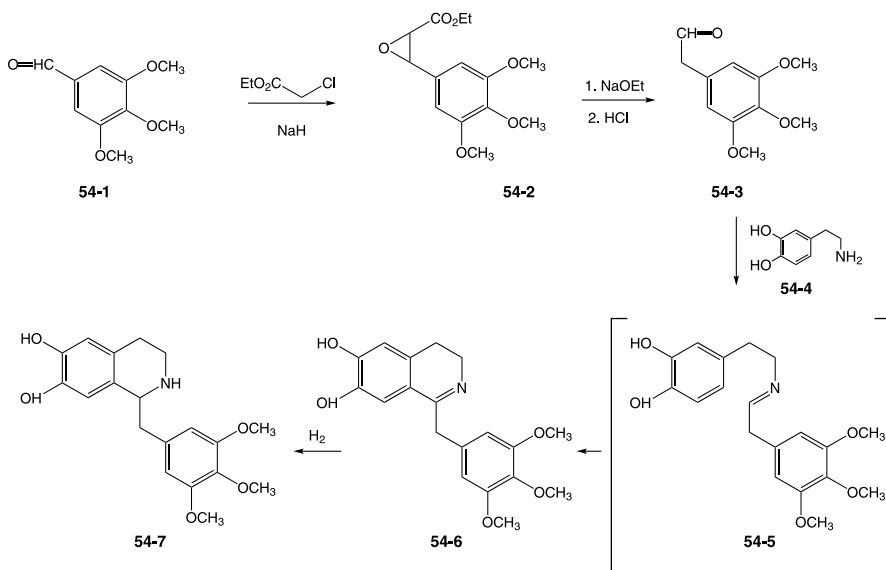
Pictet–Spengler reaction on 3,4-dimethoxy-β-phenethylacetamide provides the starting material (**55-1**) for a tetrahydroisoquinoline. The reaction in this case is in fact used as a means for placing an acetyl group *ortho* to the alkyl side chain since a different strategy is used to form the final heterocyclic ring. Reaction of the imine (**55-1**) with acetic anhydride leads to acylation on nitrogen and a shift of the double bond to the exocyclic position to give (**55-2**). Hydrolysis of this anhydro form of a carbinolamine *N*-acetate leads to a ring opening and the formation of the acetophenone (**55-3**). Base-catalyzed aldol condensation with *para*-chlorobenzaldehyde (**55-4**) gives the benzal derivative (**55-5**). Treatment of that intermediate with a strong acid leads first to the hydrolysis of the amide function; the newly freed primary amine then condenses with the carbonyl group to form an imine and thus the dihydroisoquinoline (**55-6**). Catalytic hydrogenation is then used to reduce both the side chain double bond and the imine function. The resulting secondary amine (**55-7**) is then methylated by any one of several methods such as reaction with formalin and formic acid. There is thus obtained **methopholine** (**55-8**) [64], a weak opioid analgesic agent. Note that the structure of this compound follows the requirements posited by the Becket-Casy proposal (see Chapter 7).
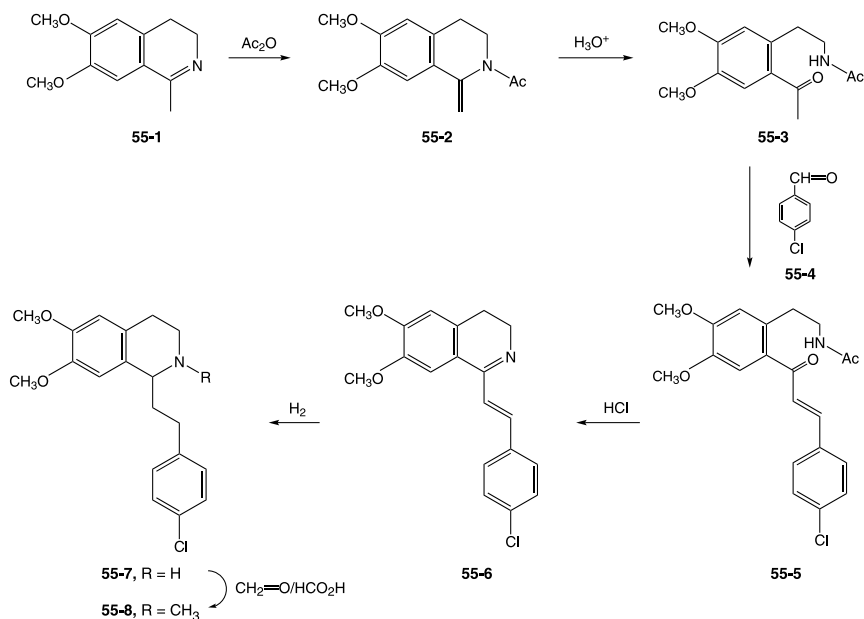
A commercial NSAID and some of its analogues that depend on an enolized heterocyclic ring for an acidic proton are considered in more detail later in this chapter. The preparation of a simplified example starts by conversion of homophthalic acid (**56-1**) with ammonia to its imide (**56-2**). Reaction of that product with *para*-chlorophenylisocyanate (**56-3**) in the presence of triethylamine results in the addition
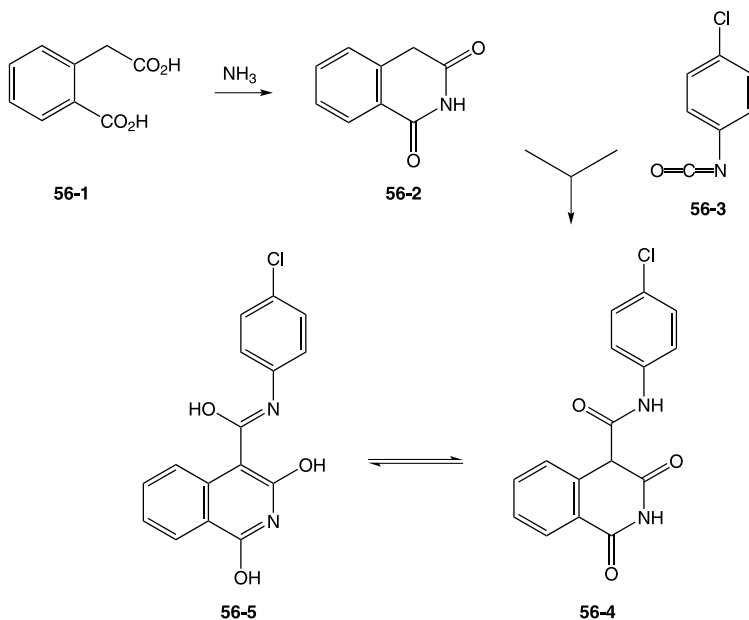
of the anion to the cumulene to give the amide [65]. The product, **tesicam**, is shown as both the full keto (**56-4**) and enol (**56-5**) tautomers that would be expected to be in very mobile equilibrium. The multiple intermediate forms that can be visualized probably contribute to the acidity of the compound.

The same isoquinoldione nucleus forms a significant part of the structure of the aldose reductase inhibitor **minalrestat** (**57-8**). The synthesis involves as the first step nucleophilic aromatic displacement of bromine in the carboxylic acid (**57-1**) by the anion from dimethyl malonate in the presence of cuprous bromide (**57-2**). The free carboxylic acid in the product is then converted to its acid chloride (**57-3**). Reaction with the benzylamine (**57-4**) in the presence of trithylamine probably leads initially to the benzamide. The presence of a base then causes the amide nitrogen to displace the methoxide from one of the adjacent ester groups to close the ring yielding (**57-5**). Carbonate-catalyzed alkylation with bromoacetonitrile proceeds on the ring carbon flanked by two carbonyl groups to afford (**57-6**). The newly introduced nitrile is then hydrolyzed in a strong acid to the corresponding amide (**57-7**). The anion from the reaction of the amide with sodium hydride displaces the remaining ester function to form the spiro-amide (**57-8**) [66]. The presence of a quaternary center in the product, **minalrestat**, precludes keto-enol tautomerism.
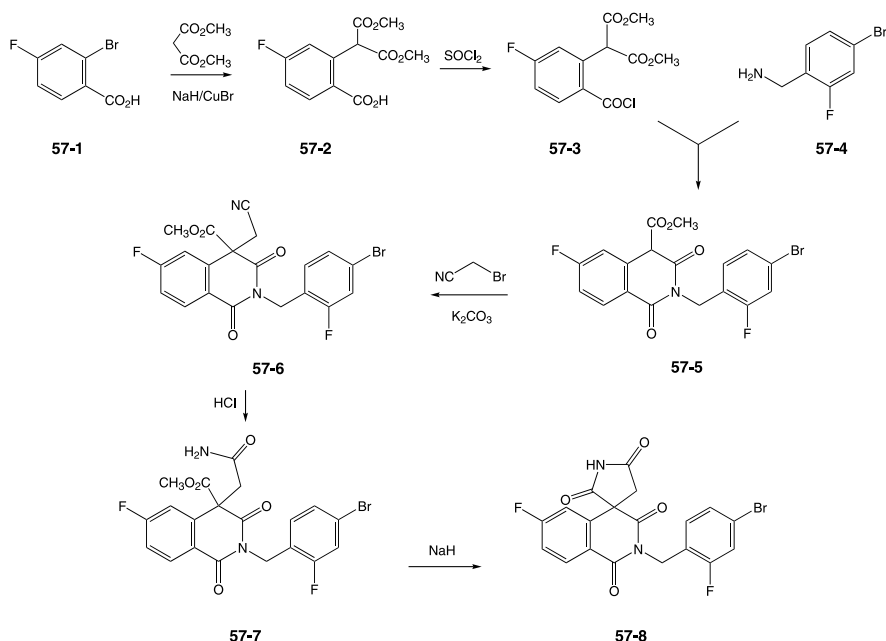
11.2. COMPOUNDS THAT CONTAIN TWO HETEROATOMS

11.2.1. Benzodioxans

The majority of the small number of biologically active compounds based on a fused ring system that includes two oxygen atoms consist of 1,4-benzodioxans. All but one

of the compounds discussed below, interestingly, interact with the adrenergic system. The simplest **piperoxan** (**58-5**) [67] was in fact one of the first α-blockers to be studied in any detail. The synthesis of this compound illustrates one of the standard entries into this heterocyclic system. Condensation of catechol (**58-1**) with epichlorohydrin in the presence of an aqueous base can be visualized as proceeding initially with the epoxide (**58-2**) formed by either the direct displacement of chlorine or ring opening of the oxirane followed by the displacement of chlorine by the resulting alkoxide to form a new epoxide. Attack by the phenoxide anion on the side chain epoxide in (**58-2**) leads after neutralization to the key intermediate (**58-3**). Reaction of that product with thionyl chloride leads to the corresponding chloro derivative (**58-4**). Displacement of the newly introduced halogen with piperidine affords **piperoxan** (**58-5**). Guanidine derivatives were among the first drugs to be used as antihypertensive agents. The use of these agents was accompanied by a host of side effects attributed to the fact these agents acted as sympathetic blockers. Preparation of a guanidyl benzodioxane antihypertensive agent starts with a small variation of the scheme above; the alcohol (**58-3**) is first converted to its mesylate; displacement with guanidine then affords **guanoxone** (**58-6**) [68].
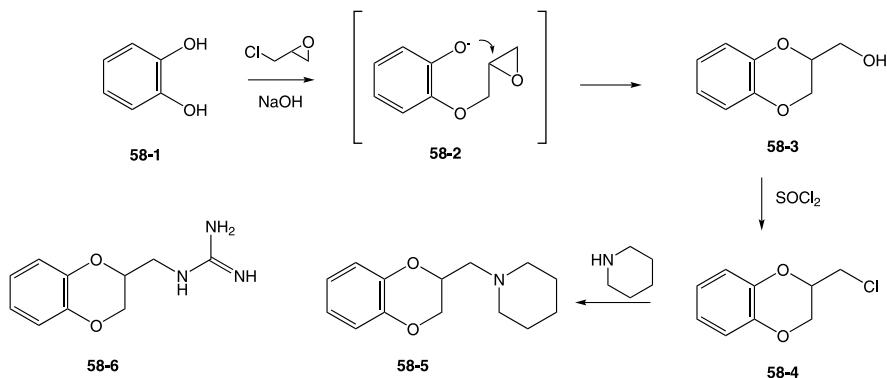
A more fundamental variation of this scheme leads to a benzodioxan that contains an oxirane side chain that can be used for subsequent elaboration. The use of salicylaldehyde (**59-1**) as a starting material instead of catechol simplifies the initial alkylation step. Thus reaction of that with 1,4-dichloro-2-butene leads to the ether (**59-2**) of unspecified configuration. Reaction of the product with peracid leads to both the epoxidation of the olefin and a Bayer–Villiger scission of the aldehyde to give the formate (**59-3**). Saponification of the ester with a mild base initially affords the alkoxide (**59-4**). This then undergoes a chain of epoxide opening and closing reactions to give the product (**59-5**). This compound, it should be noted, is an oxygenated analogue of the intermediate (**13-4**) used for the synthesis of nebivolol (**13-5**), described earlier in this chapter. Proceeding in an analogous fashion, reaction of (**59-6**) with a calculated amount of benzylamine affords the product of reaction of two epoxides with a single benzyl amine; reductive removal of the benzyl protecting group affords the β-blocker **bendacalol** (**59-7**) [69].
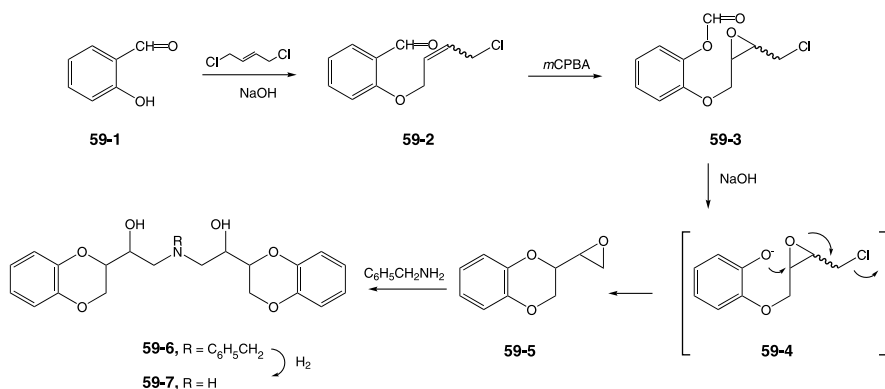
A rather simpler compound includes both a benzodioxan nucleus and the imidazoline function associated with α-adrenergic agonists such as **clonidine**. As in the standard approach for preparing imidazolines, the treatment of nitrile (**60-1**) with alcoholic hydrogen chloride leads to the iminoether (**60-2**). Reaction of that intermediate with ethylenediamine then affords **idazoxin** (**60-3**) [70], a compound that interacts with α-adrenergic receptors.
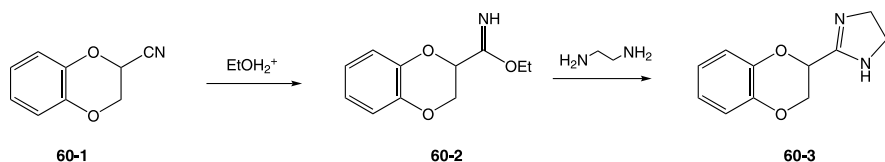
Attachment of a base-bearing side chain to the carbocyclic ring of a benzodioxan gives another compound that acts as an α-adrenergic blocker. Mannich reaction of the methyl ketone in (**61-2**), obtainable by acetylation of the benzodioxan proper (**61-1**), with phenylpyrrolidine (**61-3**) and formaldehyde leads directly to **proroxan** (**61-4**) [71].
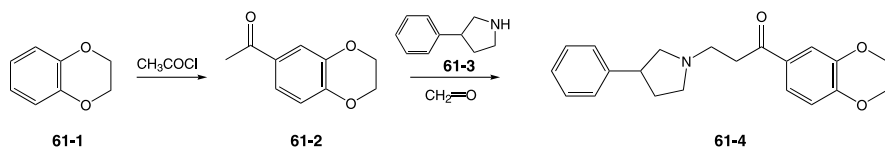
The benzodioxan ring also serves as the aromatic moiety for one of the ubiquitous analogues of the "spirone" anxiolytic agents discussed in Chapter 9. In the absence of a specific reference, the requisite intermediate (**62-1**) could be obtained by reducing the cyano group in nitrile (**60-1**) with lithium aluminum hydride. Alkylation with the "spirone" side chain chloride (**62-2**) would then afford **binospirone** (**62-3**).

60-1   62-1   62-2   62-3
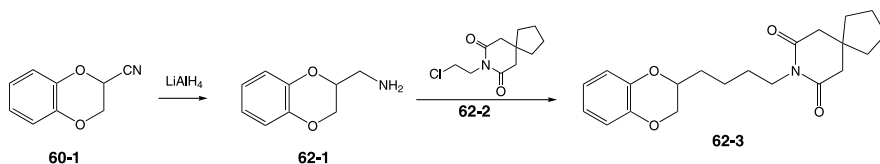
11.2.2. Miscellaneous Fused Rings That Include Oxygen

Variously substituted quinolines and acridines account for almost all antimalarial agents. The development of resistance to these drugs by strains of the parasite has led to a widespread search for compounds for treating malaria from other structural classes. The original lead for quinine came from folkloric use; it is thus perhaps fitting that a new class owed its origin to the Chinese' use for many years of the standing plant product Quinhao for treating malaria. The poor biopharmaceutical properties of the active ingredient, arteminsin (**63-1**), led to programs for identifying more suitable analogues. Though the structure of the active analogue **arteflene** (**63-7**) does not exactly match the criteria for this section, its chemistry is sufficiently inter-esting to merit discussion. The enantioselective synthesis starts with the chiral com-pound (**63-2**) derived from d-carvone. Reaction of that compound with the ylide from ethyltriphenylphosphonium bromide takes place selectively at the more electrophilic methyl ketone to afford the olefin (**63-3**). Photolysis of that product in oxygen in the presence of a sensitizer leads to the formation of the bridged bicyclic peroxide (**63-4**). The reaction may be rationalized by assuming the addition of singlet oxygen to the isolated double bond, which shifts to the end of the ethyl group in the process.

63-1   63-2   63-3   63-4   63-5   63-6   63-7
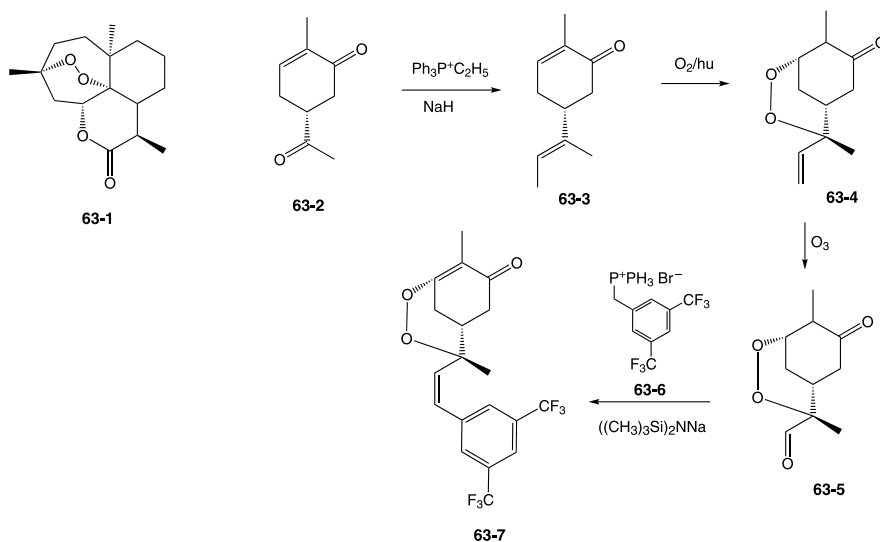
The thus-formed peroxide then adds to the end of the eneone. Ozonization of the terminal olefin then leads to the aldehyde (**63-5**). The newly formed carbonyl group is then reacted with the ylide from phosphonium salt (**63-6**) under salt-free conditions. This results in the addition of the *bis*-trifluoromethylbenzyl moiety with *cis* geometry about the double bond. There is thus obtained **arteflene** (**63-7**) [72].

A wide variety of heterocylic systems have shown enough activity as non-nucleoside reverse transcriptase inhibitors (NNRTI) against HIV. The structure of the benzoxazine inhibitor **efavirenz** (**64-10**) differs significantly from the earlier agents by its relative simplicity. Acylation of *para*-chloroaniline (**64-1**) with pivaloyl chloride affords the corresponding amide (**64-2**). Treatment with butyl lithium followed by ethyl trifluoroacetate introduces the required trifluoroacetyl group (**64-3**). Acid hydrolysis then removes the pivaloyl group to afford the free amine (**64-4**). That function is then protected from reagents in the rest of the sequence by alkylation with paramethoxybenzyl chloride (**64-5**) to afford the amide (**64-6**). The key reaction in the sequence involves the stereospecific addition of the cyclopropyl-acetylene moiety. Thus, addition of the lithium acetylide from cyclopropylacetylene to the trifluoromethylcarbonyl group in (**64-6**) in the presence of the substituted ephedrine derivative (**64-7**) proceeds with high enantiomeric excess. Reaction of the thus-obtained aminoalcohol (**64-8**) with phosgene closes the benzoxazine ring (**64-9**). The methoxybenzyl group is then removed under reductive conditions. This last reaction affords **efavirenz** (**64-10**) as a single enantiomer [73].
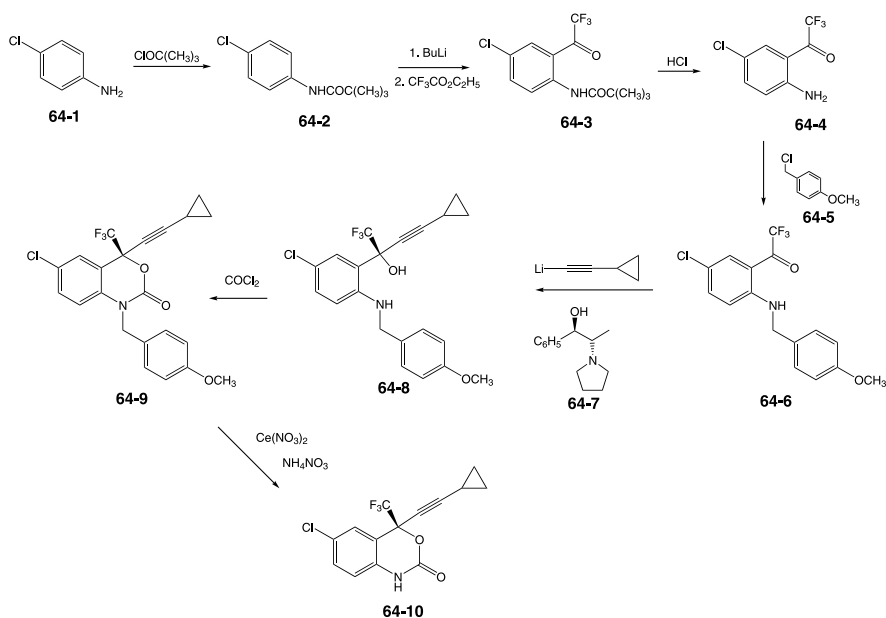
11.2.3. Cinnolines and Phthalazines

Internal diazonium coupling provides the key reaction in the preparation of two cinnolines that have been investigated as potential therapeutic agents. Treatment of the 2-amino-acetophenone (**65-1**) with nitrous acid leads to the corresponding diazonium salt (**65-2**), depicted as its enol tautomer. Attack by the diazonium group onto the electron-rich enol leads to coupling and the formation of the 4-hydroxycinnoline derivative (**65-3**). Reaction of that compound with bromine leads to aromatic halogenation and the formation of bromide (**65-4**). Nucleophilic aromatic displacement of halogen by means of cyanide gives the corresponding nitrile (**65-5**). Alkylation of the anion from treatment of the intermediate with a strong base takes place, as in the case of the analogous quinolols, on nitrogen to form the *N*-ethyl cinnolone (**65-6**). Hydrolysis of the nitrile to the carboxylic acid affords **cinoxacin** (**65-7**) [74], an antibiotic that can be viewed as an aza analogue of the more familiar quinolones.
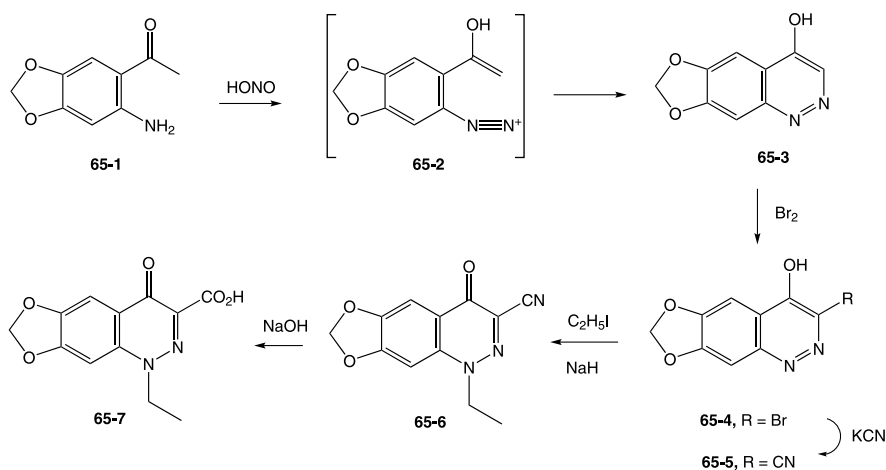
Pyrrazolones formed by the reaction of alkylmalonates with 1,2-diarylhdrazines provide the heterocyclic nucleus for NSAIDs related to **phenylbutazone** (see Chapter 8). The same function is provided in a somewhat more complex NSAID in which the arylhydrazine function is embedded in a partly reduced cinnoline. The preparation of this agent starts with the conversion of aminobenzophenone (**66-1**) to its corresponding methyl carbinol with methylmagnesium bromide followed by acid-catalyzed dehydration to the methylene derivative (**66-2**). The diazonium salt (**66-3**) obtained on reaction of the product with nitrous acid undergoes internal coupling when treated with ammonium hydroxide to give the cinnoline (**66-4**). Catalytic reduction probably proceeds by initial 1,4-addition of hydrogen; the product then spontaneously rearranges to the hydrazine derivative (**66-5**). Condensation of that intermediate with diethyl *n*-amylmalonate leads to a fused pyrrazolone; there is thus obtained **cintazone** (**66-7**) [75].
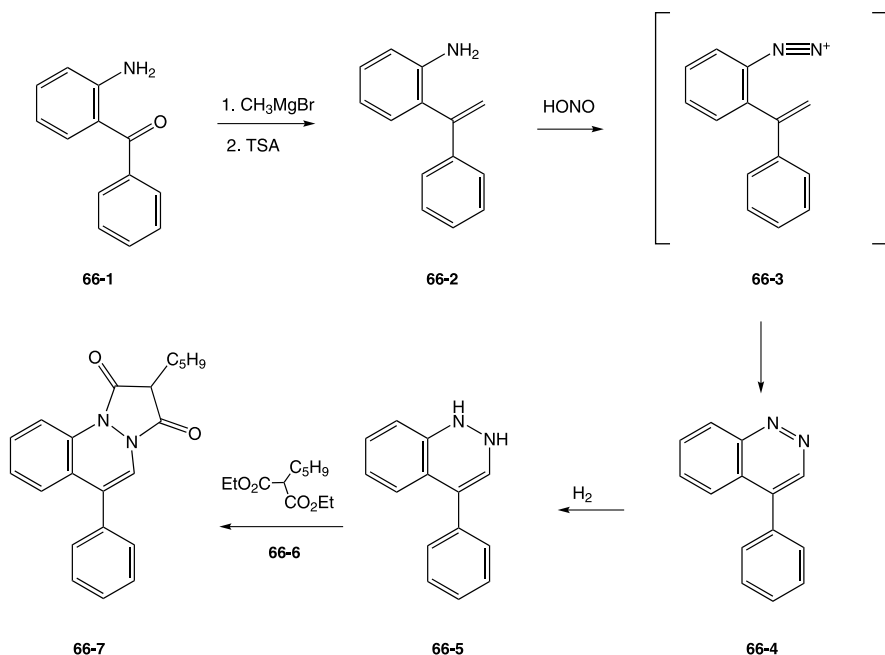
Dihydralazine (**67-3**) is the less important of the two phthalazine antihypetensive agents; its preparation is however recorded first because of its simplicity. Thus, reaction of phthalhydrazide (**67-1**) with phosphorus oxychloride leads to the by now very familiar conversion of the amide functions to enol chlorides (**67-2**). The displacement of halogen by hydrazine leads directly to the antihypertensive agent **dihydralazine** (**67-3**) [76].

The preparation of a monosubstituted phthalazine hinges on the differing oxidation states of the starting carbonyl groups. Thus reaction of acid-aldehyde (**67-4**) with **hydrazine** gives an intermediate (**67-5**) that contains a hydrazone as well as a
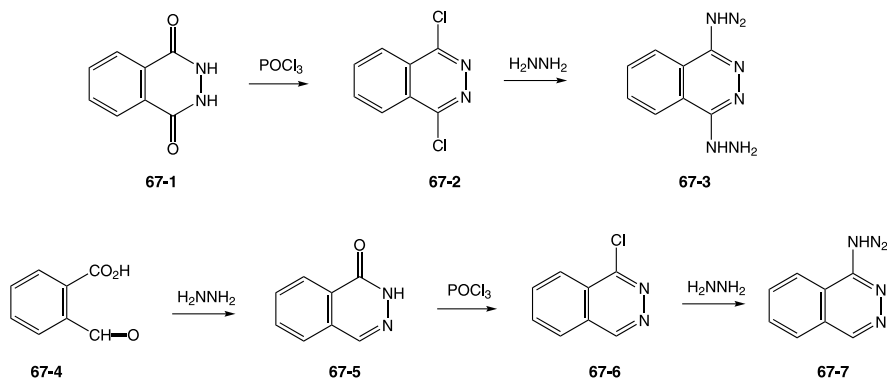
hydrazide group. Exposure to phosphorus oxychloride converts the latter to an enol chloride to give the monofunctional derivative (**67-6**). Hydrazinolysis of this intermediate leads to **hydralazine** (**67-7**) [76]. This antihypertensive agent, as well as its disubstituted analogue, have been shown to be direct-acting vasodilators by their relaxing effect on vascular smooth muscle. These drugs were at one time one of the mainstays for treating elevated blood pressure but have now been largely displaced by some of the more specific anrihypertensive drugs.

Replacement of the hydrazine function by a substituted 4-piperidinol leads to a compound that has been investigated as a cardiotonic agent that acts by increasing the contractile force of cardiac smooth muscle. The preparation is quite analogous to those above. The key step involves the displacement of chlorine from the substituted chlorophthalazine (**68-1**) with the ethyl carbamate from 4-piperidinol (**68-2**) to afford the alkylation product **carbazeran** (**68-3**) [77].
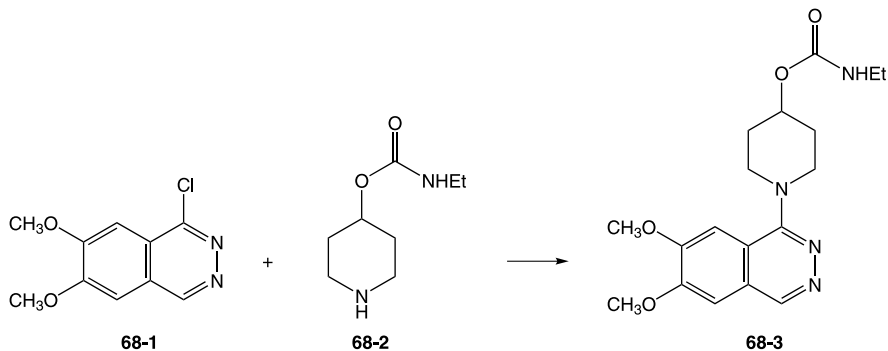
Several therapeutic agents are based on phthalazinone nuclei, in which the hydrazide carbonyl group persists in unmodified form. Reaction of keto-acid (**69-1**) with hydrazine leads to the phthalazinone (**69-2**). Alkylation of the hydrazide nitrogen with 2-(chloroethyl)-*N*-methylpyrrolidine (**69-3**) surprisingly leads to the incorporation of a seven-membered azepine ring rather than the expected ethylpyrroldine. This can be explained by keeping in mind that it is likely that the
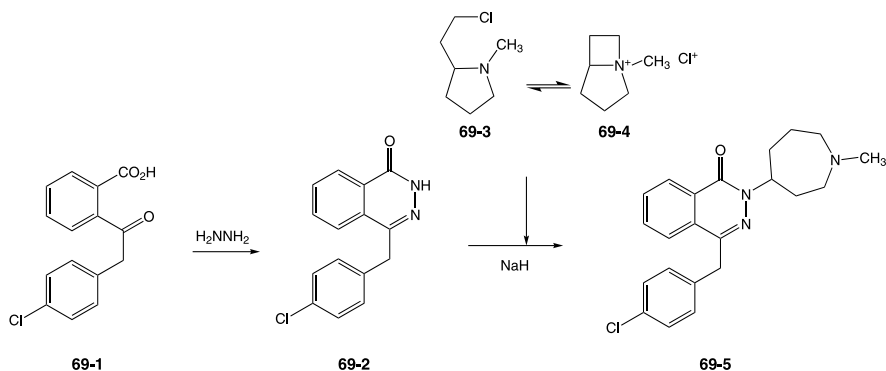
starting alkylating agent (**69-3**), like many other 2-chloroethyl nitrogen mustards, exists, to some extent, in equilibrium with the cyclized quaternary form (**69-4**). Attack at the bridgehead opposite the ammonium ion with a simultaneous ring opening will lead to the observed product; this affords the H_1 antihistamine **azelastine** (**69-5**) [78]. The cyclic form of the simpler *N*-chlroethyl amines, the so-called mustards, which correspond to (**69-4**), consists of the aziridinium salts. The product from the reaction of this species with nuclophiles is in this case identical with that from the direct displacement of halogen from the open form.

Reaction of phthalic anhydride (**70-1**) with the ylide from ethyl triphenylphos-phoniumacetate leads to the condensation product (**70-2**), which in effect consists of a cyclic enol anhydride. Treatment of this product with hydrazine leads to the hydrazone-hydrazide (**70-3**). Alkylation of the anion from removal of the hydrazide proton with the substituted benzyl bromide (**70-4**) affords the alkylation product (**70-5**). Saponification then leads to the aldose reductase inhibitor **ponalrestat** (**70-6**) [79].
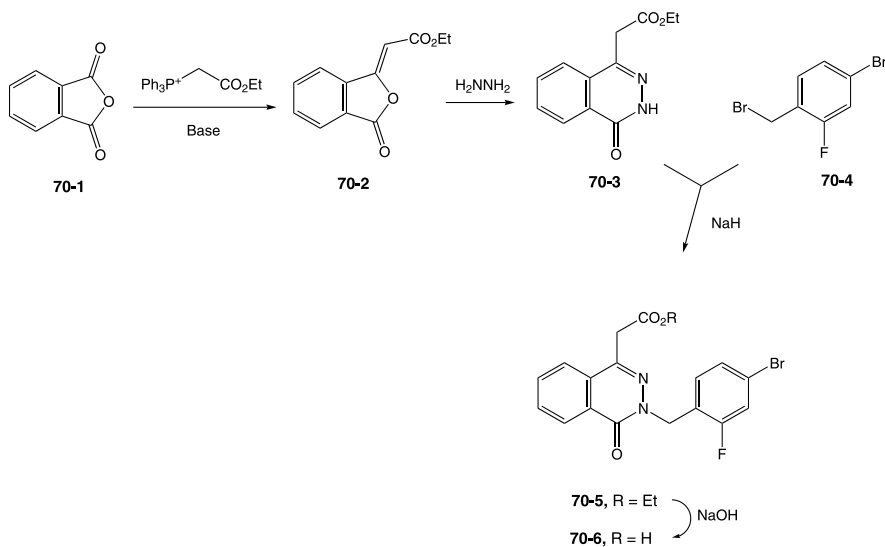
The more complex phthalic anhydride (**71-1**) is the starting point in the synthesis of a phthalazinone-based platelet aggregation inhibitor. Reaction of that compound with malonic acid in pyridine involves as the first step a ring opening of the anhydride by malonate anion and the formation of the keto-acid from the acylation of malonic acid. The resulting product spontaneously loses carbon dioxide to afford the transient intermediate (**71-2**). This β-keto-acid then undergoes a second loss of carbon dioxide to afford the methyl ketone (**71-3**). This intermediate is actually isolated in its pseudoacid form (**71-4**). The methyl group is then subjected to carefully controlled oxidation with potassium permanganate to give the keto-acid (**71-5**). Reaction with hydrazine proceeds in a straightforward manner to give the phthalazinone (**71-6**).

The carboxylic acid is then converted to its ester with ethanol in the presence of an acid. Carboxylic esters are not, in the normal course of events, reduced by sodium borohydride. The presence of an adjacent imine nitrogen apparently changes the resistance to that reagent. Thus, treatment of (**71-7**) with sodium borohydride leads to a selective reduction of the ester on the heterocyclic ring to an alcohol while leaving that on the benzene ring unaffected. There is thus obtained **oxagrelate** (**71-8**) [80].
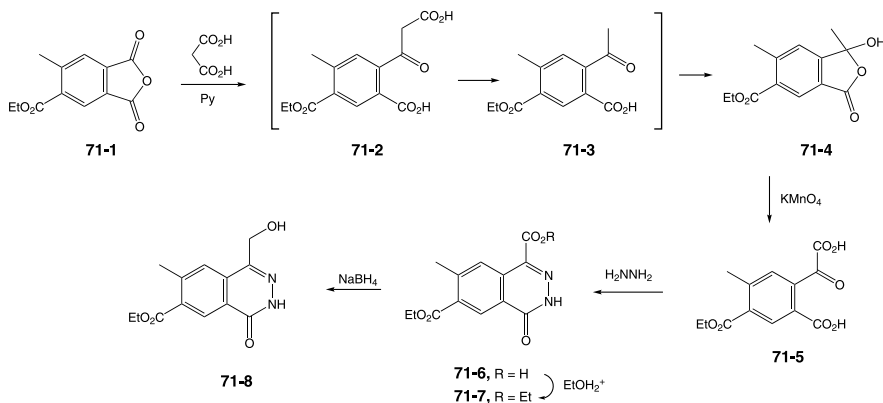
11.2.4. Quinazolines

A number of compounds based on the 6,7-dimethoxyquinazoline nucleus have shown effects on cardiovascular function or act as bronchodilators. The simplest and earliest of these agents, **quazodine** (**72-3**), has been investigated as a vasodilator, as a cardiotonic agent, and as a bronchodilator. It became clear from later work that it probably acts as a phosphodiesterase (PDE) inhibitor. The very effective aminoquinazoline-based antihypertensive agents that were developed later, on the other hand, act as α-adrenergic blockers. Methods for forming the quinazoline ring system closely parallel those used for the monocyclic pyrimidines. The preparation of that first compound thus involves as the first step the formation of formamide (**72-2**) by reaction of the anilino-ketone (**72-1**) with a mixture of formic acid and acetic anhydride. Treatment of the amide with ammonia then leads to the quinazoline and thus **quazodine** (**72-3**) [81].
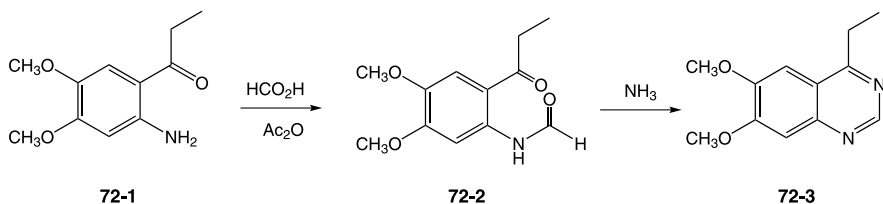
Incorporation of a piperazine function on the heterocyclic ring leads to a compound in which bronchodilator activity predominates. Treatment of the amino-amide (**73-1**) with trimethyl orthoformate provides the additional carbon atom for the formation of the quinazolone ring in (**73-2**). Reaction with phosphorus oxychloride in effect converts the ring to its aromatic form (**73-3**) by locking in the former amide as an enol chloride. Displacement of the halogen with the isobutyryl urethane (**73-4**) from piperazine affords **piquizil** (**73-5**) [82].
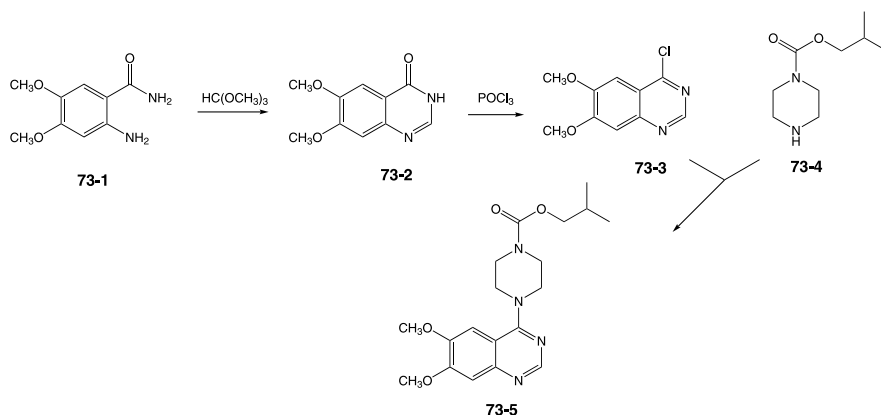
It sometimes happens that novel drugs lead to the discovery of new pharmacological principles; the science of pharmacology did, it needs be kept in mind, have its origin in the study of the biological effects of drugs. Up to the advent of **prazocin** (**74-5**), it had been accepted that the side effects observed with α-adrenergic blockers, such as an increase in heart rate and water retention, were due to reflex compensatory responses. The detailed examination of the mechanism of action of the new drug revealed that it, too, lowered blood pressure by blocking vasoconstriction due to α-adrenergic stimulation. This work also led to the finding that the drug interacted with a subset of receptors that did not cause the classic compensatory effects. Many additional subclasses of α-, and for that matter β-adrenergic receptors, it
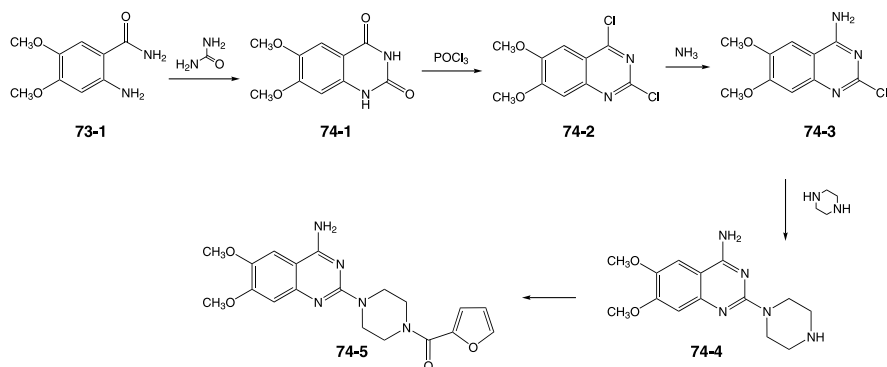
should be noted, have been identified since. Condensation of amino-amide (**73-1**) with urea supplies the additional carbon atom in the form of a carbonyl group to afford the quinazolodione (**74-1**); the ubiquitous phosphorus oxychloride reaction then converts that to the dichloride (**74-2**). The halogen on the carbon next to the aromatic ring is apparently significantly more reactive than that at the 2 position, so that treatment of the intermediate with ammonia at room temperature results in selective displacement of that halogen to afford (**74-3**). Reaction of that product with piperazine under more strenuous condition leads to replacement of the remaining chlorine and the formation of (**74-4**). Acylation of that intermediate with furoyl chloride then affords the antihypertensive drug **prazocin** (**74-5**) [83].

As the antihypertensive agent prazocin came into widespread use, reports began to accumulate of relief experienced by men who were taking this drug who had urinary problems associated with enlargement of the prostate. Detailed pharmacology then revealed that α-2 sympathetic receptors occur in the prostate. The relief from symptoms of benign prostatic hypertrophy (BPH) is now attributed to the blockade of those receptors. This discovery was followed by the introduction of compounds targeted specifically at this new indication. The α-2 blocker **alfuzocin** (**75-5**) shares the quinazoline moiety with prazocin and some of its later analogues. The synthesis of the side chain on this agent starts with the acylation of amine (**75-1**) with the ethoxycarbonate derivative (**75-2**) of tetrahydrofuroic acid to afford amide (**75-3**). Hydrogenation then reduces the cyano group to the corresponding primary amine (**75-4**). Reaction of the side chain (**75-4**) with the quinazoline (**74-3**) leads to the displacement of the remaining ring halogen on the quinazoline. There is thus obtained the α-2 blocker alfuzocin (**75-5**) [84].
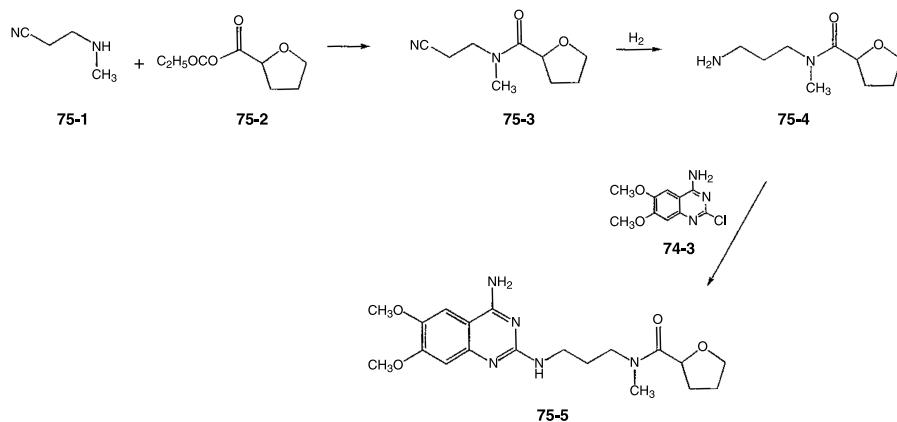
The synthesis for the starting material (**76-1**) for another of these α-2 blockers is quite analogous to that used for the dimethexoxy quinazoline (**74-3**). In this case, the remaining chlorine is displaced with the complete prefabricated side chain, the piperazine urethane (**76-2**). There is thus obtained **trimazocin** (**76-3**) [85].

76-1   76-2   76-3
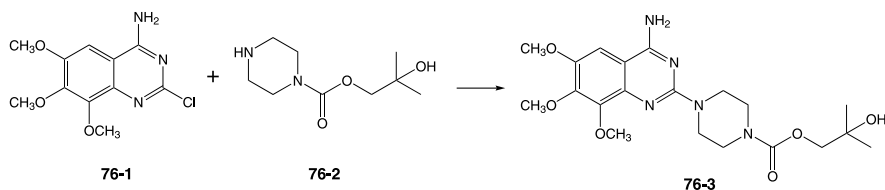
Condensation of anthranilic acid (**77-1**) with an iminoether represents another method for preparing quinazolones. The reaction with the iminoether (**77-2**) from 2-cyano-5-nitrofuran and ethanolic acid can be visualized as proceeding through the formation of the amidine from addition-elimination of anthranilic acid; cyclization then affords the observed product (**77-3**). This is then converted to chloride (**77-4**) in the usual way. Displacement of the newly introduced chlorine with diethanolamine leads to the formation of **nifurquinazol** (**77-5**) [86], one of the antibacterial nitrofurans (see Chapter 8).

77-1   77-2   77-3

POCl₃

77-5   77-4
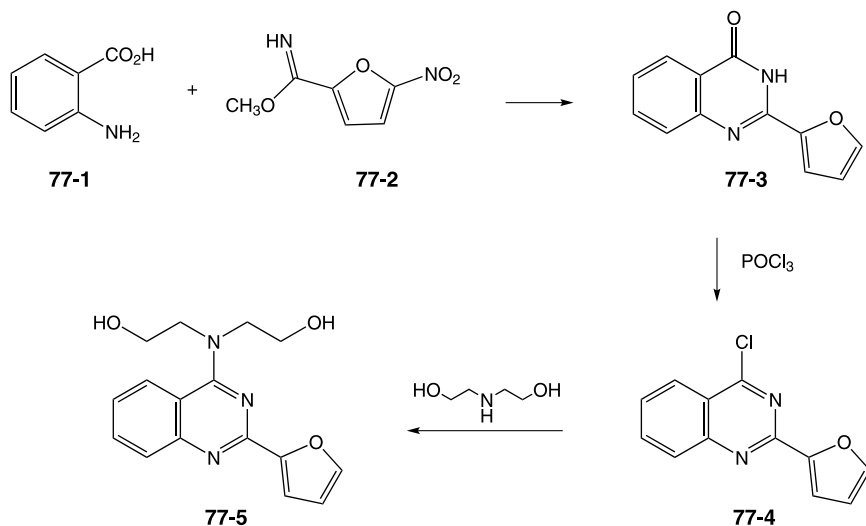
The particularly good activity against protein kinases of α-aminoquinazoline derivatives is borne out by their activity against both *in vitro* and *in vivo* models of human tumors. The examples that follow are but two of a number of compounds from this structural class that have emerged from the focus that has been devoted to this structural class. Nitration of the benzoate (**78-1**) with nitric acid affords the nitro derivative. Hydrogenation converts this to the anthranilate (**78-2**). In one of the standard conditions for forming quinazolones, that intermediate is then treated with ammonium formate to yield the heterocycle (**78-3**). Reaction of this last product with phosphorus oxychloride leads to the corresponding enol chloride (**78-4**). Condensation of this last intermediate with meta-iodoaniline (**78-5**) leads to displacement of chlorine and the consequent formation of the aminoquinazoline

(**78-6**). Reaction with the trimethylsylil derivative of acetylene in the presence of tetrakis-triphenylphosphine palladium leads to the replacement of iodine by the acetylide. Tributylammonium fluoride then removes the silyl protecting group to afford the kinase inhibitor **erlotinib** (**78-7**) [87].
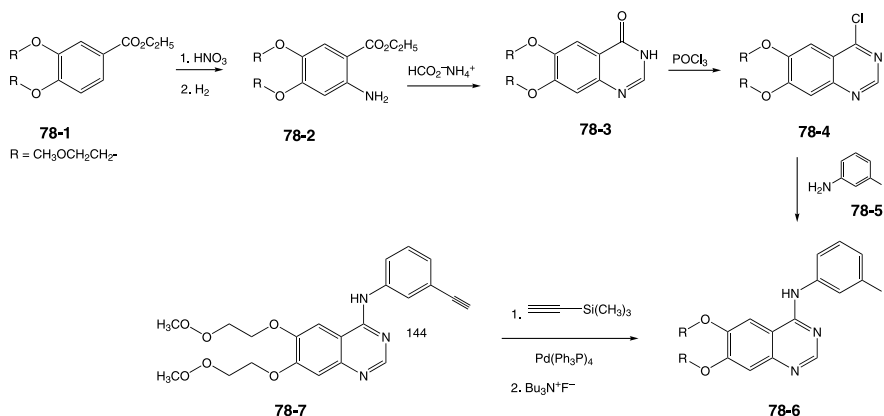
Aliphatic nitrogen replaces the anilide attached to the heterocyclic ring found in most of the other compounds in this class. Alkylation of the phenolic function in (**79-1**) with 3-chloropropyl tosylate affords the ether (**79-2**) from displacement
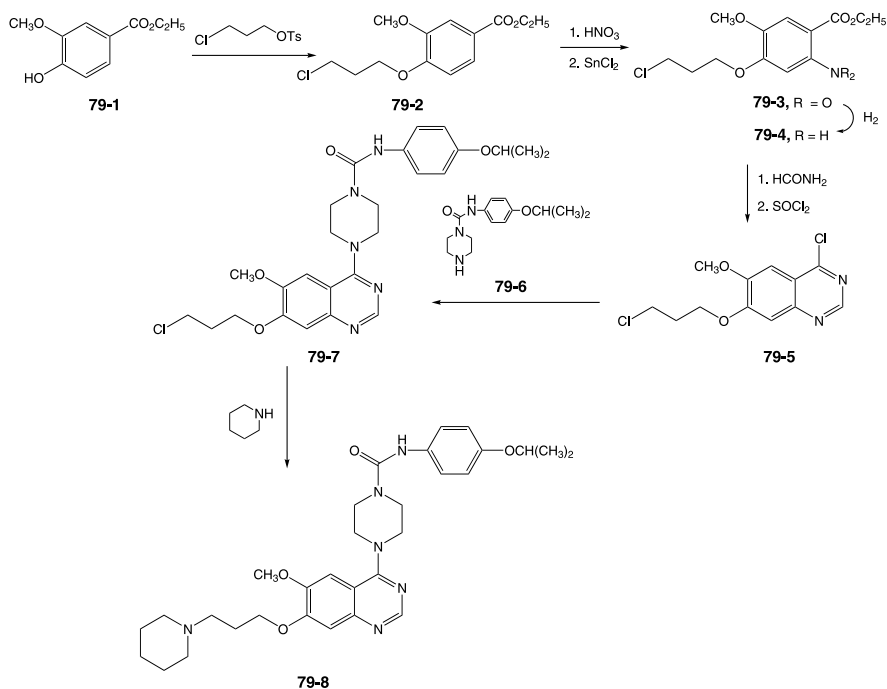
of the tosyl group. Reaction with nitric acid gives the ortho nitro derivative (**79-3**). Catalytic hydrogenation then reduces this to the corresponding amine (**79-4**). Treatment of this intermediate with formamide then adds the requisite atoms for forming the quinazoline ring. The carbonyl group is then converted to the enol chloride (**79-5**) by means of thionyl chloride. The sequence departs from previous schemes by the use of an alycyclic amine in the next step. Thus, the reactive enol halogen atom is displaced by the free amine in a mono-acylated piperazine (**79-6**) to afford (**79-7**). Reaction of the product with piperidine under somewhat more forcing conditions replaces the terminal chlorine on the ether-linked side chain to complete the synthesis of **tandutinib** (**79-8**) [88].

The use and design of inhibitors of folate synthesis as antitumor agents was discussed in detail in Chapter 8, in connection with relatively simple monocyclic folate mimics. Bicyclic compounds that more closely resemble the pteridine in the endogenous compounds would be expected to have at least as good activity as the simpler analogues. The quinazoline **trimetrexate** (**81-2**), which contains in addition an aromatic side chain that takes the place of the PABA moiety of folic acid, is under study as a cancer chemotherapy drug. Reaction of the nitrile (**80-1**) with guanidine can be envisaged as proceeding initially with the arylguanidine (**80-2**) that results from the displacement of chlorine activated by electrons withdrawing nitro and cyano groups. The addition of one of the guanidine amines to the nitrile will then lead to the diaminoquinazoline (**80-3**). The nitro group is then reduced to the amine (**80-2**) by any of several methods as, for example, stannous chloride in hydrochloric acid. It should be noted that the two amino groups on the quinazoline ring are virtually nonbasic; treatment of (**80-4**) with nitrous acid thus proceeds selectively on the newly introduced anilino group. Reaction of the thus-produced diazonium salt with cuprous cyanide results in the formation of the corresponding nitrile (**80-5**) [89]. The same reaction sequence starting with the benzonitrile containing a 5-methyl group will give (**80-1**).
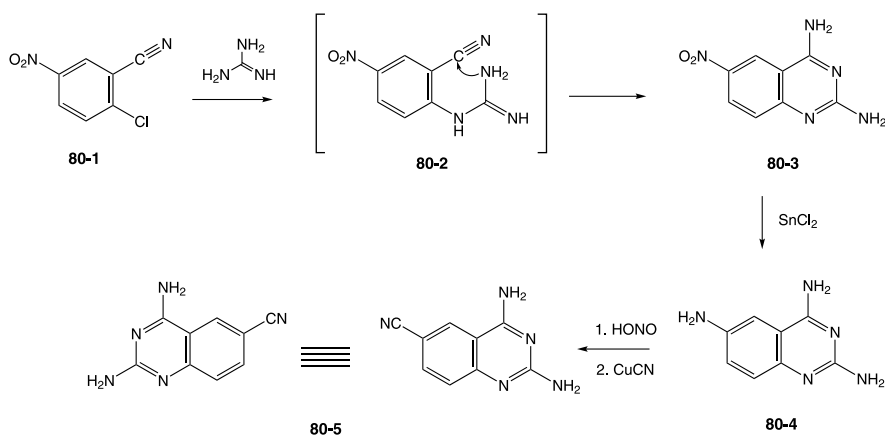
The final step in the sequence consists of the hydrogenation of the nitrile (**80-5**) in the presence of trimethoxaniline (**81-1**) over Raney nickel. A number of possibilities

can account for this exchange of bases; the aniline could, for example, add to an intermediate imine from the nitrile followed by a loss of ammonia from the resulting aminal. This reduction-exchange reaction affords **trimetrexate** (**81-2**) [90].
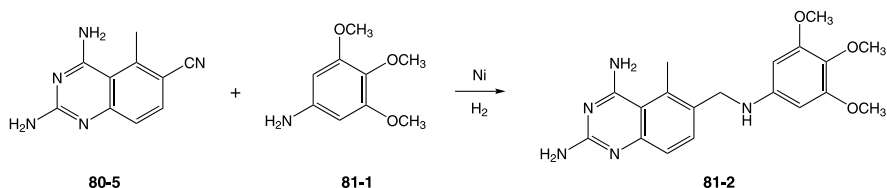
11.2.5. Quinazolones

The structure of the folate antagonist **ralitrexed** (**82-9**) more closely resembles the endogenous cofactor, though it omits nitrogen in the ring next to the pyrimdine and replaces the benzene ring of the PABA fragment with thiophene. The synthesis of this compound starts with the condensation of the anthranilic acid (**82-1**) with ethyl iminoacetate to form quinazolone (**82-2**). Reaction of that intermediate with *N*-bromosucinimide leads to the bromination of the methyl group (**82-3**) [91]. In a convergent sequence, ethyl glutamate (**82-5**) is acylated with the nitrothiophene acid chloride (**82-4**) to afford the amide (**82-6**). Catalytic hydrogenation next reduces the nitro group to afford the corresponding amine (**82-7**). The major part of the structure is then put in place by alkylation of the newly formed amino group with the benzyl bromide (**82-3**) to afford (**82-8**). Saponification of the ester groups in this last intermediate then yield the antifolate **ralitrexed** (**82-9**) [92].
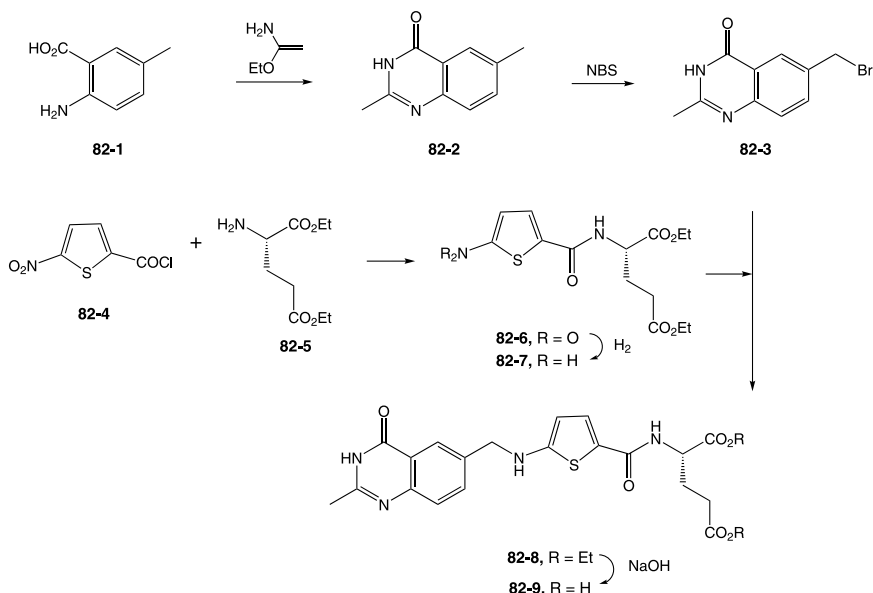
One of the first quinazolone-based drugs, the sedative hypnotic **methaqualone** (**83-4**), gained considerable notoriety as a drug of abuse under the alias "ludes" after the original tradename Quaalude. The compound is prepared in a straightforward fashion by fusion of anthranilamide (**83-1**) with *ortho*-toluidine (**83-2**) [93]; the reaction can be envisaged as proceeding via the di-amide (**83-3**).
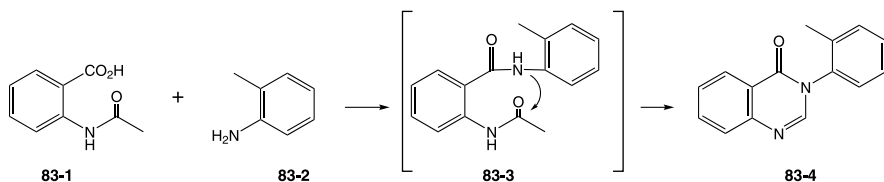
Condensation of an aminoketone with urea leads to the formation of a quinazolone by incorporation of carbonyl carbon and one amino group. Thus reaction of the aminobenzophenone (**84-1**) with urea can be rationalized by assuming the initial formation of the urea exchange intermediate (**84-2**). Cyclization will then give **fluproquazone** (**84-3**) [94], a nonopioid analgesic that shows NSAID-like activity in the absence of a typical acidic function.
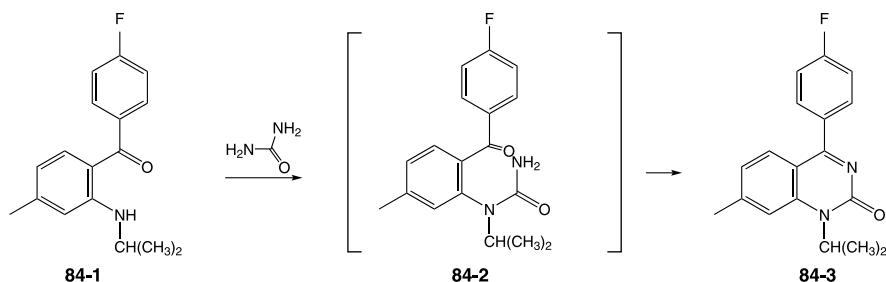
A quinazolone moiety also provides the nucleus for a highly simplified leukotriene antagonist (compare this compound with **verlukast** (**29-6**), discussed earlier in this chapter). Condensation of the anthranilate ester (**85-1**) with formamide leads to the formation of the quinazolone (**85-2**). Reaction of the salt from the reaction of this product with a strong base with ethyl 3-bromoacrylate leads to vinylation on nitrogen by what is probably an addition-elimination sequence; the product is largely the E isomer (**85-3**). Saponification then affords **tiacrilast** (**85-4**) [95].
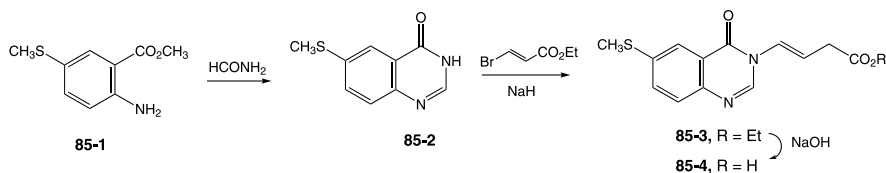
Aminoacetophenones can also act as starting materials for quinazolones. Conversion of the nitrobenzoic acid (**86-1**) to an acetophenone involves a sequence reminiscent of that used for **oxagrelate** (**71-8**). Thus reaction of the acid chloride (**86-2**) from (**86-1**) with the anion from diethyl malonate affords the tricarbonyl intermediate (**86-3**). This undergoes double decarboxylation on hydrolysis to give the methyl ketone (**86-4**). The nitro group is then reduced by hydrogenation and the resulting aniline (**86-5**) is converted to its carbamate (**86-6**). Fusion with ammonium acetate then forms the quinazolone ring. This affords **bemarinone** (**86-7**) [96], a cardiotonic agent with a somewhat atypical structure.

86-1, X = OH
86-2, X = Cl
86-3
86-4, R = O
86-5, R = H
86-6
86-7
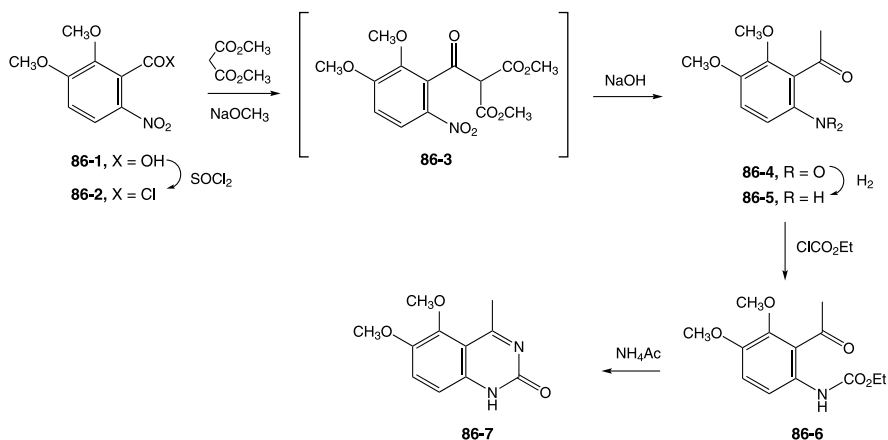
The discovery that the cyclization of one of the sulfonamide groups and the adjacent amine in classic monocyclic diuretics leads to an increase in potency is discussed in the next section. A similar increase in potency is also observed in the anthranilic acid based diuretics. Thus the fusion of anthranilic acid (**87-1**), which may show diuretic activity in its own right, with propionamide leads to the ring closure and formation of (**87-2**). Reduction of the unsaturation in the heterocyclic ring then affords the diuretic **quinethazone** (**87-3**) [97].

87-1
87-2
87-3
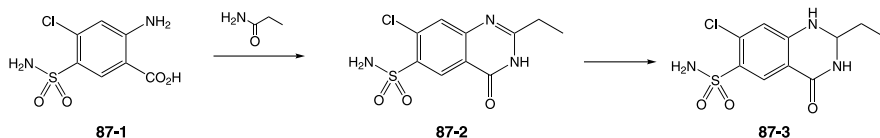
The reaction of anthranilamide (**88-1**) with benzaldehyde, in a reaction clearly modeled on the sulfonamides, can be envisaged as involving first the formation of the carbinolamine (**88-2**); displacement of hydroxyl by amino leads to the aminal and thus the diuretic agent **fenquizone** (**88-3**) [98]. The same product

would of course result from the initial formation of the carbinolamine with amide nitrogen.

88-1   88-2   88-3
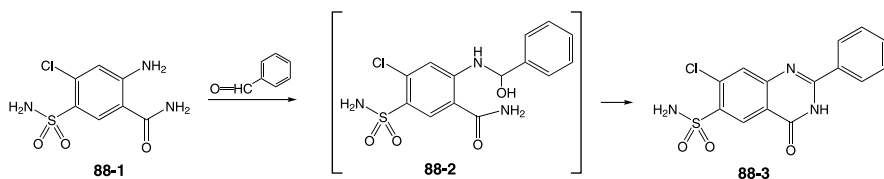
The use of activated anthranilic acid derivatives facilitates the preparation of the amides in those cases where the amines are either unreactive or difficult to obtain. Thus, reaction of (**87-1**) with phosgene gives the reactive the isatoic anhydride (**89-1**). Condensation of that with *ortho*-toluidine leads to the acylation product (**89-2**) formed with a simultaneous loss of carbon dioxide. This is then converted to the quinazolone (**89-3**) by heating with acetic anhydride. Reaction with sodium borohydride in the presence of aluminum chloride selectively reduces the double bond to yield the diuretic agent **metolazone** (**89-4**) [99].

87-1   89-1   89-2

89-4   89-3
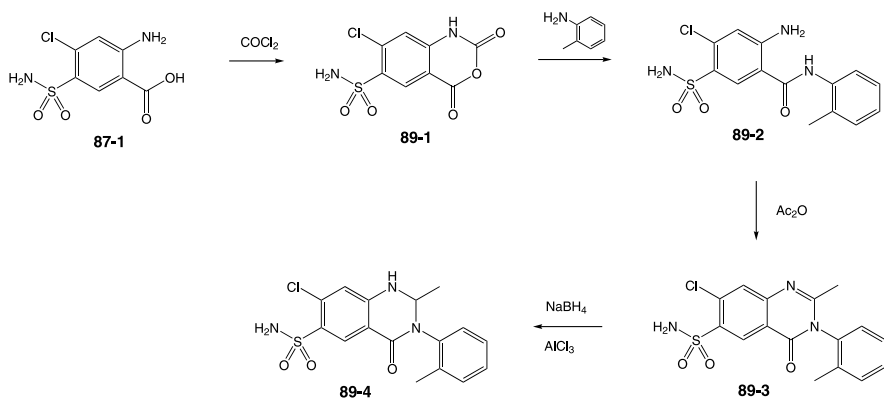
A quinazolodione provides the nucleus for yet another compound that inhibits aldose reductase. The sequence for the preparation of this agent starts with the isatoate acid (**90-1**) from 4-chloroantharanilic acid. Heating the compound with the substituted benzylamine (**90-2**) results in the formation of the ring-opened amide (**90-3**) with a loss of carbon dioxide. The ring is then reclosed, this time by reaction with carbonyl diimidazole, to afford the quinolodione (**90-4**). The anion from the reaction of this last intermediate with sodium hydride is then alkylated with ethyl bromoacetate. Saponification of the ester completes the preparation of **zenarestat** (**90-5**) [100].
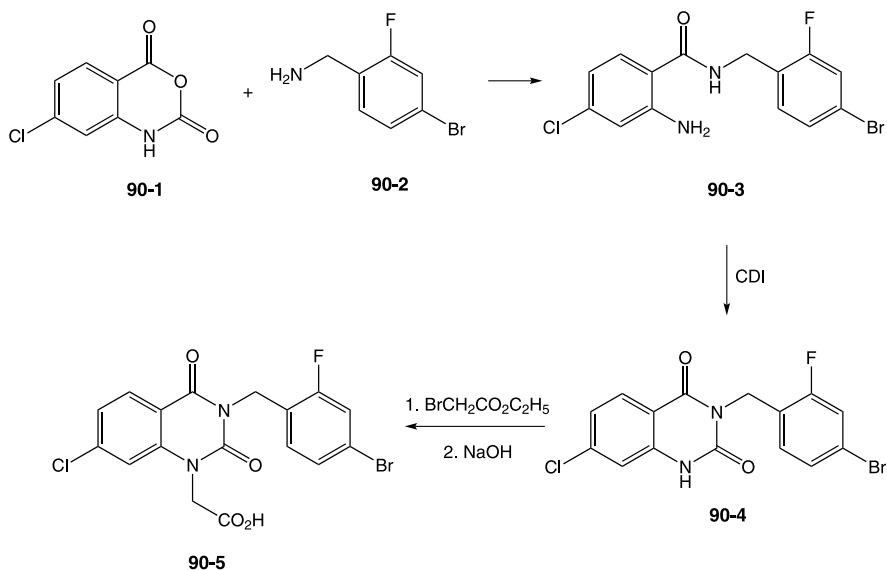
Isatoic anhydride itself (**91-1**), when allowed to react with the primary amine (**91-2**), gives the corresponding amide (**91-3**), again with the expulsion of carbon dioxide. Treatment of the intermediate with phosgene results in the formation of a quinazolodione ring. There is thus obtained the serotonin blocking compound **cloperidone** (**91-4**) [101], which is described as a sedative.
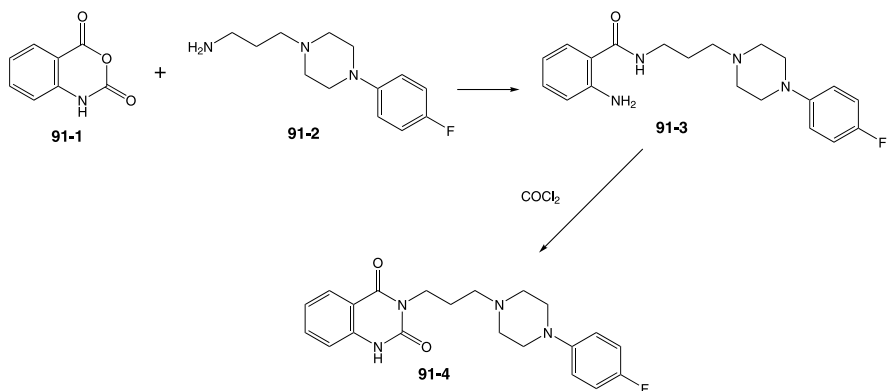
Condensation of ethyl anthranilates with isothiocyanates provides entry to a closely related compound in which the carbonyl at the 2 position is replaced by a thione. The sequence starts with the alkylation of pyrrolidine nitrogen in (**92-1**) with 2-bromoethylamine. Reaction of the primary amine in the product (**92-2**) with thiophosgene leads to the isothiocyanate derivative (**92-3**). Reaction of that reactive intermediate with methyl anthranilate (**92-4**) leads initially to the transient

addition product (**92-5**). This then undergoes the customary internal ester exchange reaction to form the heterocyclic ring. There is thus obtained the serotonin antagonist **altanserin** (**92-6**) [102].
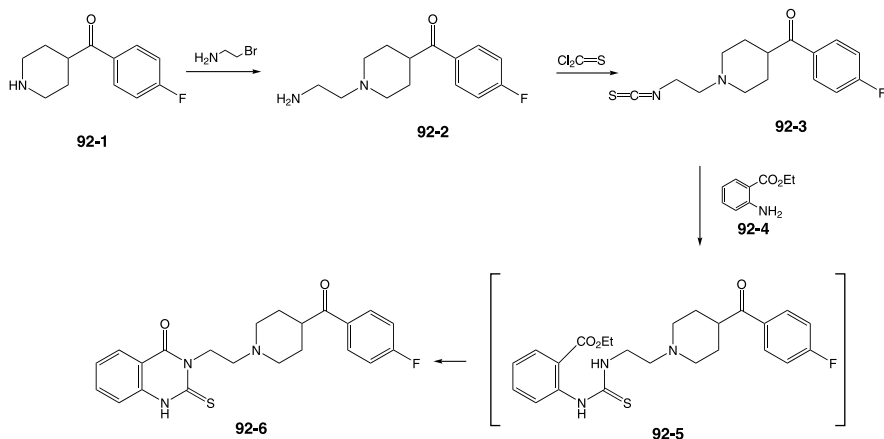
The cyclooxygenase inhibiting activity manifested by COX-1 NSAIDs, as has been noted, would seem to depend on the presence in the molecule of a group capable of supplying an acidic proton. The great majority of these drugs, as exemplified by the "profen" aliphatic acids and the "fenamate" benzoic acid derivative, incorporate a carboxylic acid. The acidity of appropriately substituted dicarbonyl groups, as noted above in connection with **tesicam** (**56-5**), can approach that of the more
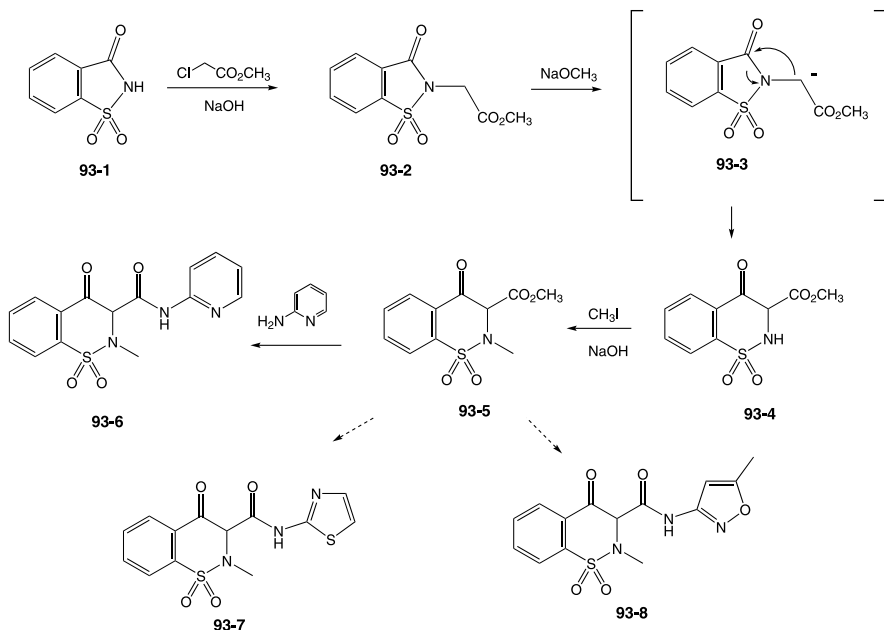
common carboxylates. An important series of NSAIDs incorporates a β-ketoamide function built into a 1,2-benzothiazine oxide ring. The synthesis of the heterocyclic nucleus begins with the base-catalyzed alkylation of saccharin (**93-1**) with methyl chloroacetate. Treatment of the product (**93-2**) with sodium methoxide leads to the formation of a carbanion on the newly introduced side chain. This anion (**93-3**) then undergoes a ring expansion reaction, part of which involves an internal Claisen reaction with simultaneous bond migration. The product (**93-4**) now contains the desired β-dicarbonyl function. Alkylation of that product with methyl iodide and sodium hydroxide interestingly occurs on nitrogen to give (**93-5**), due to the greater acidity of the sulfonamide compared to the carbonyl enolate. Heating of that product with 2-aminopyridine leads to the exchange and formation of the amide. There is thus obtained the NSAID drug **piroxicam** (**93-6**) [103]. Two closely related analogues are obtained by varying the heterocyclic amine used in this last step; 2-aminothiazole thus leads to **sudoxicam** (**93-7**) while 3-amino-5-methylisoxazole affords **isoxicam** (**93-8**).

11.3. COMPOUNDS THAT CONTAIN THREE HETEROATOMS

The fact that solid tumors are poorly supplied with blood vessels limits the effectiveness of traditional cytotoxic agents. Attempts have been made to take advantage of this hypoxic environment by designing drugs that are nonreactive until they are reduced to reactive species in oxygen-deficient tissues. The azaquinoxaline function in the chemotherapy agent **tirapazamine** (**94-4**) has been shown to form reactive nitroxyl radicals on reduction. The first step in the preparation, condensation of *ortho*-nitroaniline (**94-1**) with cyanamide, probably proceeds by initial addition of the reagent to aniline nitrogen to form the guanidine (**94-2**). The very basic nitrogen in that product then adds to the adjacent nitro group to close the ring (**94-3**). Treatment with hydrogen peroxide then oxidizes the remaining ring nitrogen to afford tirapazamine (**94-4**) [104].
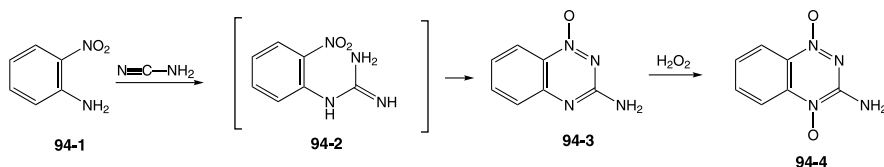
Continued research on the sulfonamide diuretic agents whose genesis from **sulfanilamide** is discussed in Chapter 2 revealed that some increase in potency was obtained by incorporating an amino group adjacent to one of the sulfonamide groups. This compound, which bears the trivial name of chloroaminophenamide, is prepared by first reacting *meta*-chlroaniline (**95-1**) with chlrosulfonic acid under forcing conditions; ammonolysis of the thus-obtained *bis*-sulfonyl chloride leads to the *bis*-sulfonamide (**95-2**) that shows somewhat improved potency over the des-amino analogue. A marked increase in potency is however observed when the

adjacent amino and sulfonamide groups are cyclized. This new functional array is analogous to the antranilamides and shows similar chemistry. Thus, reaction of (**95-2**) with formic acid leads to a benzothiadiazine [105]; this drug, **chlorothiazide** (**95-3**), was the first orally effective potent diuretic that could be used without upsetting the patient's acid–base balance.
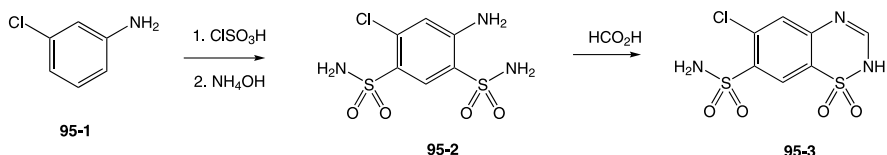
Omission of the open chain sulfonamide function interestingly suppresses diuretic activity and results in a compound that acts as a direct vasodilator. The required starting material is prepared by first displacing chlorine at the 2-position in 2,4-dichloronitrobenzene (**96-1**) by means of benzyl mercaptide to afford the thioether (**96-2**). The oxidation of sulfur by means of aqueous chlorine is accompanied by the cleavage of the sulfur carbon bond of the benzyl group. The overall reaction yields the sulfonyl chloride (**96-3**). Treatment of that with ammonia gives the corresponding sulfonamide (**96-4**). Catalytic hydrogenation then converts the nitro group to an aniline (**96-5**). Reaction of this amino sulfonamide with acetic anhydride closes the ring to afford the desired benzothiadiazine [106]. The product, **diazoxide** (**96-6**), is a very potent antihypertensive agent whose properties seem to be very similar to those of **minoxidil** (Chapter 9); there are scattered reports that this compound also stimulates hair growth.
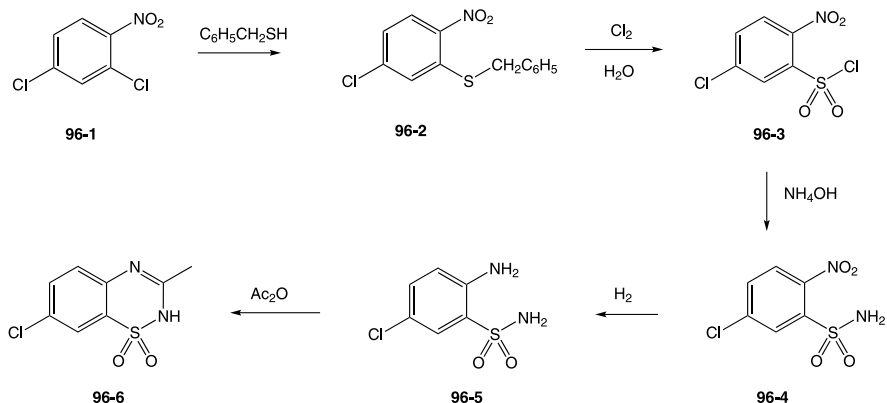
Reduction of the double bond in the heterocyclic ring of **chlorothiazide** leads to a quite unexpected major increase in potency. While methods may exist for reducing the double bond in the heterocyclic ring, the compound, **hydrochlorothiazide** (**97-2**), is in fact readily available from reaction of the aminoanthranilamide (**95-2**) by performing the cyclization with formaldehyde [107]. This reagent that can be viewed as pre-reduced version of the formic acid used to prepare chlorothiazide.

The availability of this extremely well tolerated potent diuretic agent led clinicians to investigate the possibility that elevated blood pressure could be relieved by decreasing blood volume. The drug, now better known by its initials **HCTZ**, was in fact found to be effective in lowering blood pressure in close to half of all hypertensive patients. The mechanism by which this and other thiazide diuretics make this happen is now known to be more complex than simply decreasing volume.
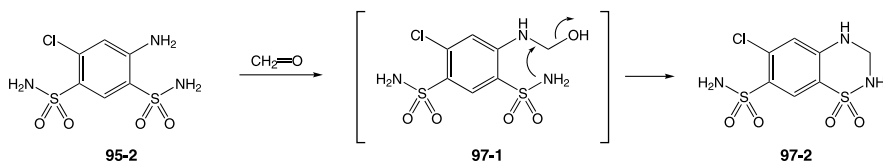
The straightforward nature of the last step combined with the uncomplicated chemistry used to prepare both the starting aminosulfonamides led to the synthesis of probably hundreds of analogues; scores of compounds were prepared with modified side chains by replacing formaldehyde with various aldehydes. A dozen or more hydrothiazides are now available to the clinician. Some of the functionality on the ring can also be modified; a temporary ring is, for example, used to insure monoalkylation on the sulfonamide nitrogen. Thus reaction of the familiar starting material (**95-2**) with urea leads to the formation of (**98-1**), which is essentially a cyclic urea. The sulfonamide nitrogen is then alkylated by means of a base and methyl iodide to give (**98-2**). Base hydrolysis of the product restores the aminosulfonamide (**98-3**), now methylated, on the sulfonamide nitrogen that will be involved in the reformation of a ring. Thus, condensation of this last intermediate with chloroacetaldehyde gives the cyclized product, the diuretic drug **methyclothiazide** (**98-4**) [108].
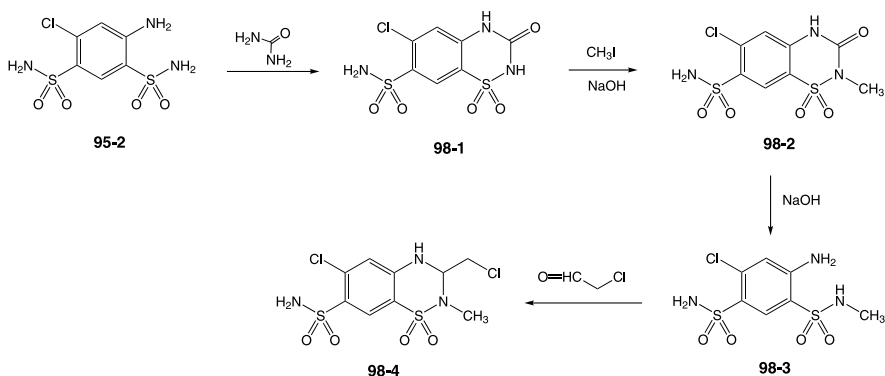
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CHAPTER 12

SEVEN-MEMBERED HETEROCYCLIC RINGS FUSED TO BENZENE

The large number of entries in the preceding chapter underlines the abundance of biologically active six-membered heterocycles fused to a benzene ring that are actually used or have been investigated as therapeutic agents. Increasing the size of the fused ring by just one carbon leads to a significant drop in the number of candidates. The benzodiazepines that form the bulk of the material in this chapter, however, represent a distinct exception to that generalization. The remarkable commercial success of this class of anxiolytic agents has led to the synthesis of literally thousands of analogues. The very small selection of compounds discussed in Section 12.2 below, which have been chosen on the basis of their chemistry, represent a very small sample of even those that have been assigned nonproprietary names.

12.1. COMPOUNDS WITH A SINGLE HETEROCYCLIC ATOM

Dopamine, the free catechol corresponding to (**1-1**), plays an important role as a neurotransmitter, particularly in the CNS. The synthesis of a dopamine-related sedative agent starts with the condensation of homoveratramine (**1-1**) with styrene oxide (**1-2**) to afford the carbinol (**1-3**). Treatment of that product with a strong acid leads to an attack on the electron-rich aromatic ring by the resulting carbocation; there is thus obtained the benzazocine (**1-4**). The secondary amine is then methylated by reaction with formaldehyde and formic acid to yield **trepipam** (**1-5**) [1].
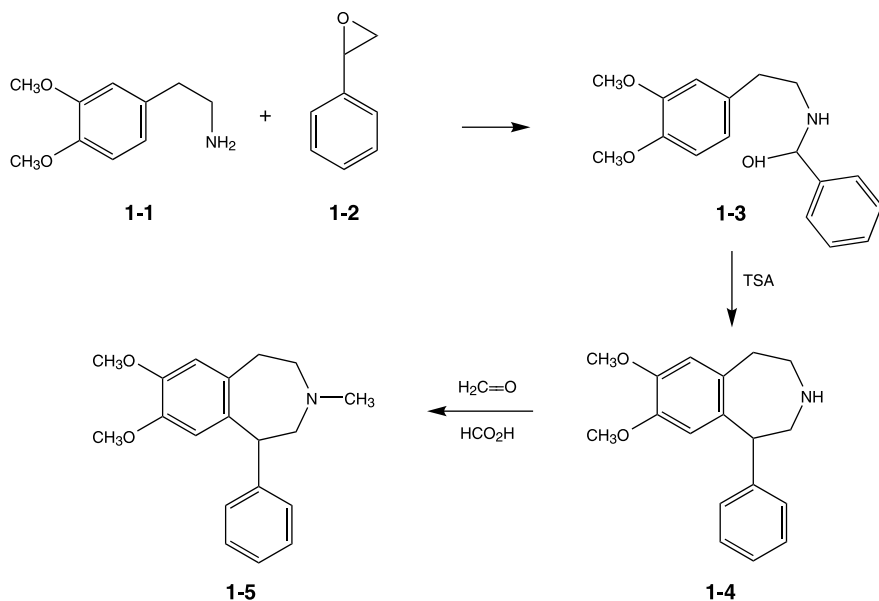
Dopamine itself has long been used as an inotropic agent in acute treatment of congestive heart failure. Both that compound and a number of its analogues have a positive action on contractility as a consequence of their adrenergic agonist activity.
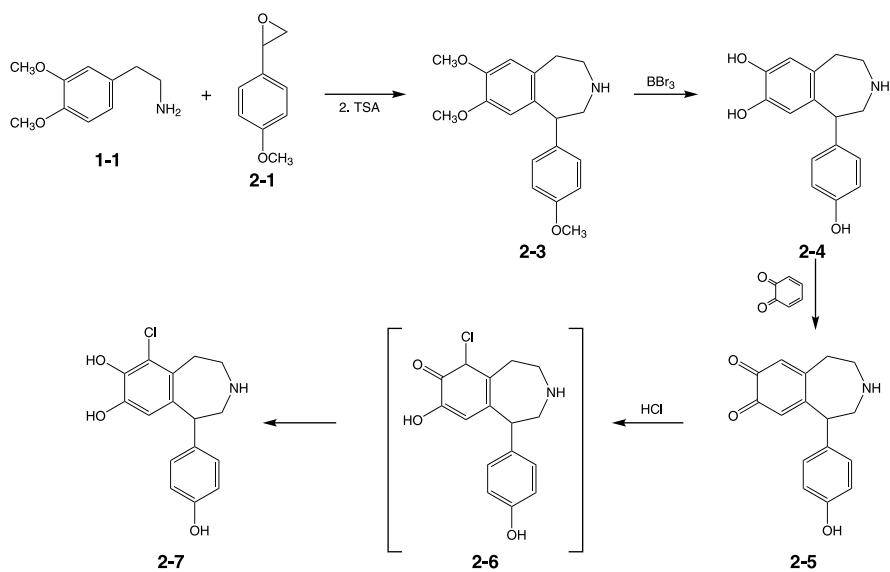
Experimental data that suggest differential biological effects for different dopamine conformers have led to extensive investigations of rigid analogues of that drug. Cardiovascular activity interestingly predominates in a close analogue of (2-7) that more closely resembles dopamine by including free phenols and a secondary amine. A condensation and cyclodehydration sequence similar to that above but using substituted 4-methoxystyrene oxide (2-1) leads to the benzazocine (2-3). Treatment of that compound with at least four equivalents of boron tribromide, one for each Lewis acid present, leads to the cleavage of the methyl ethers to free phenols to give the product (2-4). The catechol function is then oxidized selectively to the corresponding *ortho*-quinone (2-5) by a redox exchange with *ortho*-quinone itself. The addition of hydrogen chloride to the quinone can be envisaged as proceeding through a 1,4-addition intermediate such as (2-6). Enolization with the consequent aromatization then affords the dopamine agonist **fenoldapam** (2-7) [2].

The addiction to nicotine that makes smoking withdrawal so difficult for many is believed to be mediated by a subset of nicotinic acetylcholine receptors. A bridged bicylcic aryl-benzepine that acts as a partial agonist at those sites is now approved as an aid for tobacco smoking withdrawal. The synthesis starts with the known benzonorbornenone (3-1). Treatment of that compound with selenium dioxide leads to the oxidation of the carbon adjacent to the carbonyl group and thus the formation
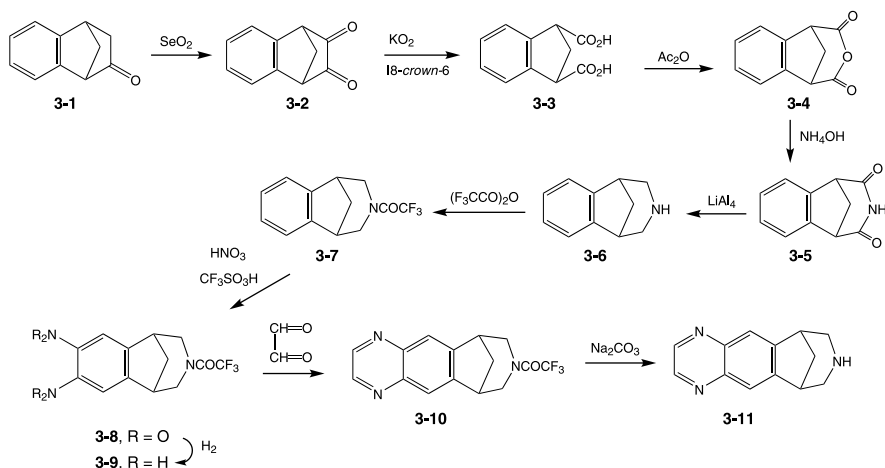
of the α-diketone (3-2). Further oxidation with potassium superoxide in the presence of a crown ether cleaves the diketone to afford the dicarboxylic acid (3-3). This intermediate is then activated by conversion to the anhydride (3-4) by means of acetic anhydride. Reaction with ammonia then leads to the imide (3-5). Reduction with lithium aluminum hydride then takes the carbonyl group to methylene to give the key intermediate, benzazepine (3-6) [3]. The secondary amine is next protected as a triflate (3-7) by means of trifluoroacetic anhydride. Nitration under rather drastic conditions, with nitric and trifluormethylsulfonic acids, results in the addition of two nitro groups (37-7). The newly introduced functions are then reduced

catalytically to give the α-diamine (**3-9**). Condensation of this last intermediate with glyoxal then gives the phthalazine (**3-10**). Removal of the protecting group with a mild base completes the synthesis of **varenicline** (**3-11**) [4].

The hormone vasopressin plays an important role in the fluid accumulation that places additional strain on the weakening heart in congestive heart failure by the thus-generated excess blood volume. The common diuretics that are often used to decrease the excess fluid often upset the balance of electrolytes in the remaining fluid and can thus adversely affect kidney function. Thiazides, for example, are well known to cause excretion of potassium. A recently developed nonpeptide vasopressin antagonist has shown promising initial activity in relieving heart failure– associated fluid retention without at the same time affecting electrolyte balance. Construction of the benzapine moiety begins with the esterification of the benzoic acid (**4-1**) followed by reduction of the nitro group with stannous chloride (**4-2**).
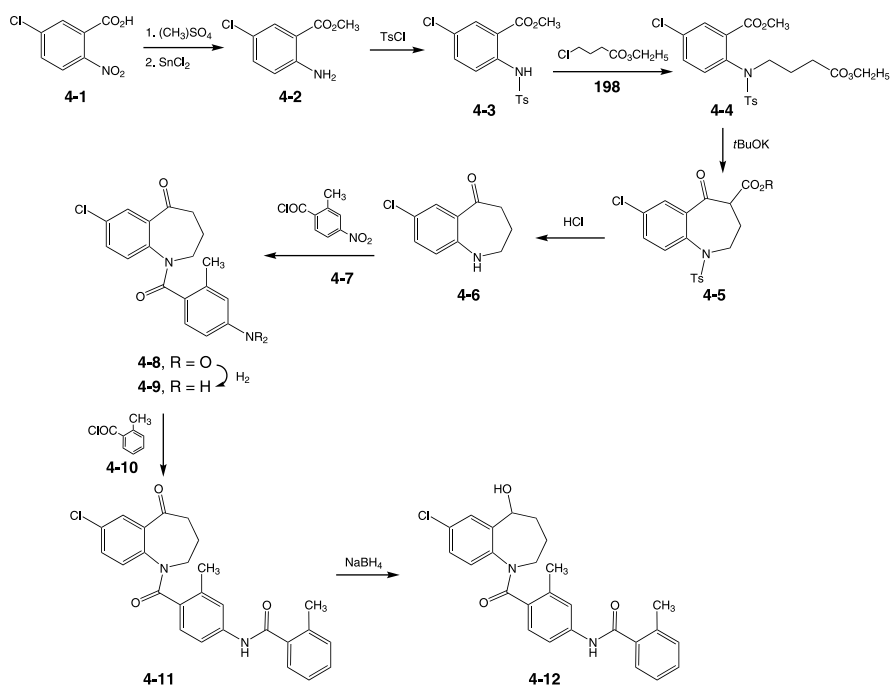
The aniline nitrogen is then converted to the *para*-toluenesulfonamide (**4-3**). Reaction of this intermediate with ethyl ω-chlorobutyrate in the presence of potassium carbonate then gives the alkylation product (**4-4**). Potassium *tert*-butoxide–catalyzed Claisen condensation of this diester leads to azepinone (**4-5**) as a mixture of methyl and ethyl esters resulting from alternate cyclization routes. A strong acid leads to the transient keto-acid, which then decarboxylates; the toluensulfonyl group is lost under reaction conditions as well as affording the benzazepinone (**4-6**). This last intermediate is then acylated with the benzoyl chloride (**4-7**) to afford amide (**4-8**).

Catalytic reduction of the nitro group proceeds to the aniline (**4-9**). The chain is next extended by acylation of the newly formed amine with ortho-toluyl chloride (**4-10**) to give (**4-11**). Reduction of the azepinone carbonyl group with borohydride affords the vasopressin antagonist **tolvaptan** (**4-12**) [5].

A benzazepine that includes the same β-ketoamide array as piroxicam (Chapter 11) retains NSAID activity. Oxidation of benzothiapinone (**5-1**), obtainable by cyclization of 4-(4-chlorophenylthio)-butyric acid, with hydrogen peroxide gives the corresponding sulfone (**5-2**). This is then converted to its enamine (**5-34**) by reaction with pyrrolidine. Condensation of the intermediate with 3,4-dichorophenylisocyanate (**5-4**) leads to the amide (**5-5**). Hydrolysis with an aqueous acid cleaves the enamine function to give the keto-amide and thus **enolicam** (**5-6**) [6].
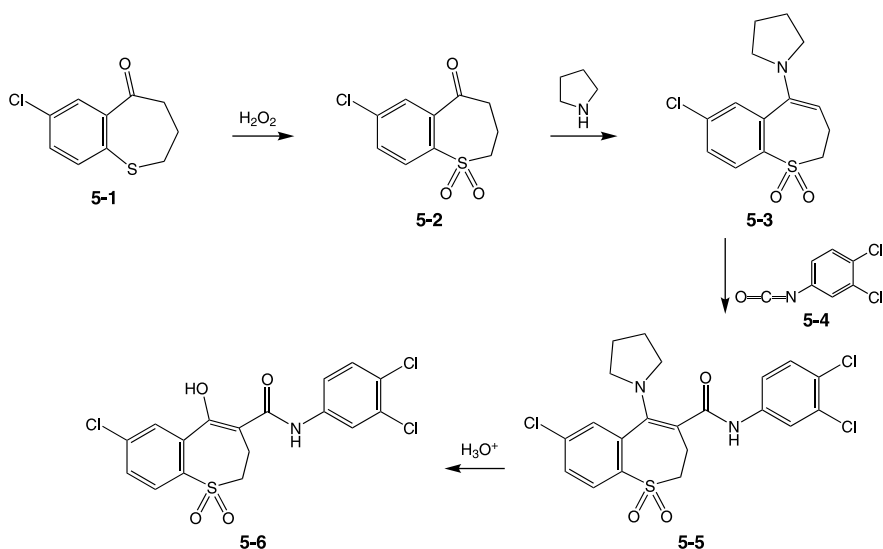
12.2. COMPOUNDS WITH TWO HETEROATOMS

12.2.1. Benzodiazepine Anxiolytic Agents

The discovery of the benzodiazepines provides one of the most apt illustrations of the role of serendipity in finding new classes of drugs. The case at hand involved first the unexpected course for two successive chemical reactions; the availability of a new mouse behavioral screen just in time to test the newly synthesized compound completed the unexpected discovery sequence. The benzodiazepines quickly gained an enormous market as antianxiety agents as hypnotics and to a lesser extent as muscle-relaxing agents. Their mood-altering properties almost inevitably resulted in their becoming a drug of abuse with the result that these drugs are now, at least in the United States, classed as controlled substances. Advances in the development of assays involving radioactively labeled ligands led to the identification, in the late

1970s, of receptors that bind benzodiazepines. This receptor, which is actually part of a complex involved in gamma aminobutyric acid (GABA) regulation, has been subsequently shown to bind structurally unrelated agents active in the CNS such as, for example, **zolpidem** (see Chapter 15).

The first starting material for building benzodiazepines was prepared inadvertently in a synthesis aimed at the benzodiazoxepine (**6-1**). The oxime acetamide (**6-2**) from 2-aminobenzophenone was thus treated with hydrogen chloride in the expectation that the new heterocycle would form by the elimination of water between the oxime and the enol form of the amide. The product turned out in fact to be the quinazoline *N*-oxide (**6-3**), the product from the addition of the nucleophilic oxime nitrogen to the amide carbonyl group.

6-1   **6-2**   **6-3**
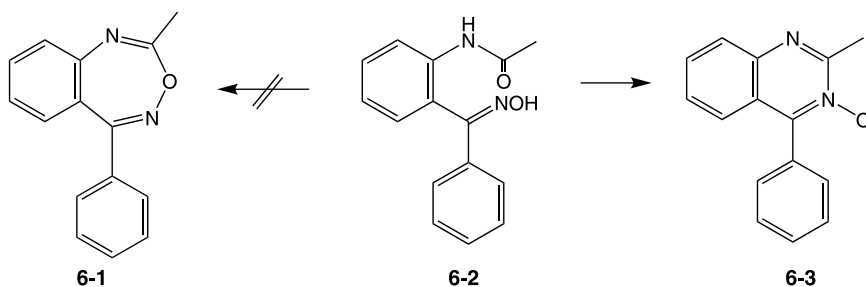
The original preparation of an arylbenzodiazepine relied on a closely related qinazoline; a large number of alternate routes have, however, been developed since [7]. Reaction of the oxime from aminobenzophenone (**7-1**) with chloroacetyl chloride gives the chloroacyl amide (**7-2**); this is converted to the corresponding quinazoline *N*-oxide (**7-3**) on treatment with hydrogen chloride. Attempted displacement of the halogen in (**7-3**) with methylamine, probably intended to provide a simple analogue for screening, gives instead a benzodiazepine. The reaction can be visualized as

7-1   **7-2**   **7-3**

7-6   **7-5**   **7-4**
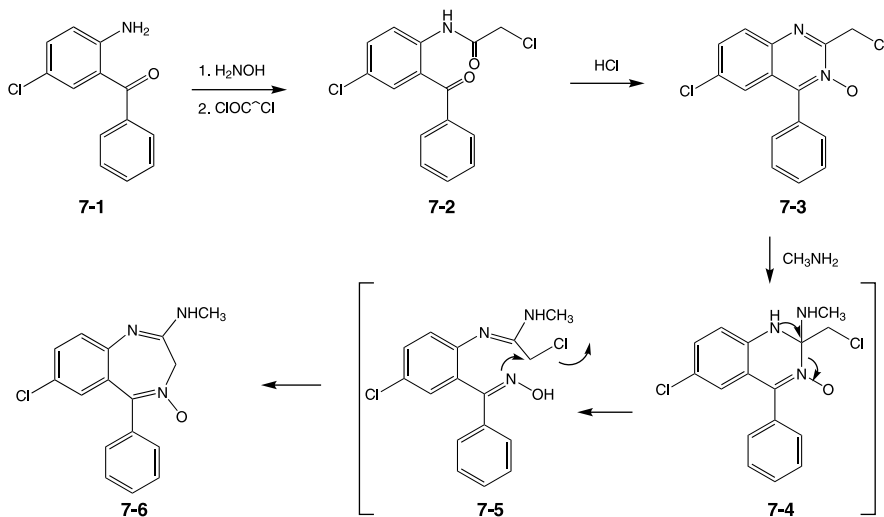
involving initially the formation of the adduct (**7-4**); the return of the electrons in ring nitrogen will then lead to a ring opening and the formation on the amidino-oxime (**7-5**). This species then undergoes internal displacement of chlorine by the basic oxime nitrogen with the consequent formation of the seven-membered ring. This affords **chlordiazepoxide** (**7-6**) [8], better known as Librium, the first of a long series of benzodiazepines.

Full activity is retained in the face of considerable structural simplification; the amidine function in (**7-6**) can thus be replaced by a simple amide. One of the more straightforward approaches to this compound involves first the acetylation of amino-benzophenone (**8-1**) with chloroacetyl chloride to give the chloromethyl amide (**8-2**). Heating this compound with ammonia or its latent equivalent, hexamethylene tetramine (HMTA), can be envisaged to involve the initial displacement of chlorine to give a glycineamide. Cyclization by imine formation then affords **diazepam** (**8-3**) [9], more familiarly known as Vallium. Support for this sequence comes from the observation that a modest yield of (**8-3**) can be obtained on heating (**8-1**) with glycine ethyl ester in pyridine [10].
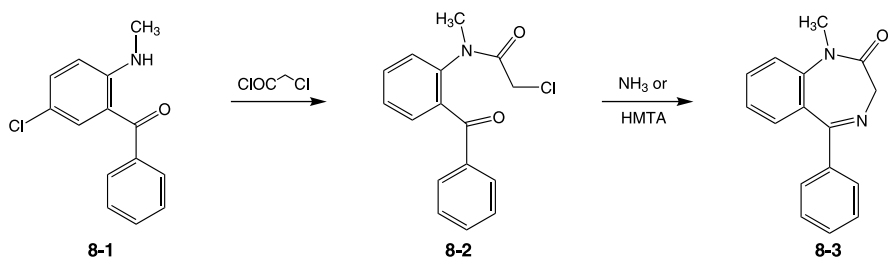
One of the more important routes for the metabolism of benzodiazepines involves the introduction of a hydroxyl group at the 3 position in the heterocyclic ring. The fact
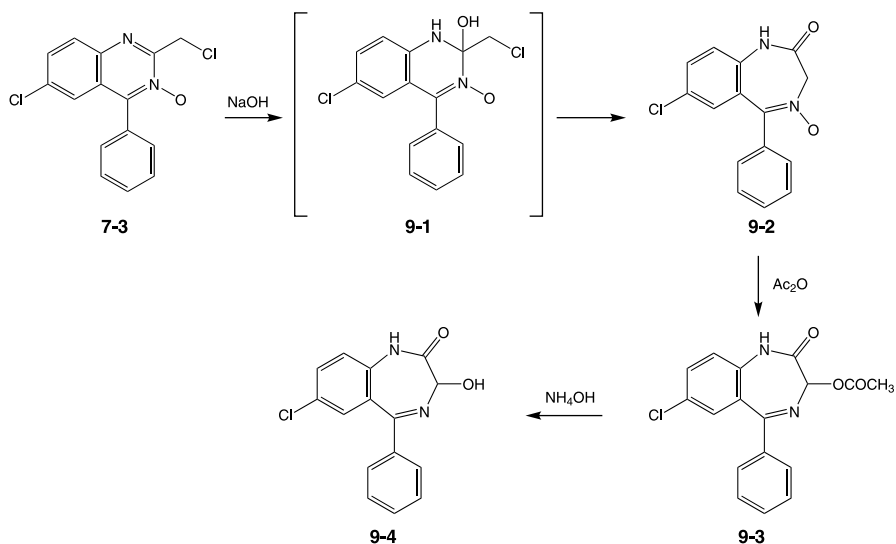
that this product shows full activity opens the possibility that it may be the proximate active species. A variant on the quinazoline *N*-oxide rearrangement provides the starting material (**9-2**) for one route to 3-hydroxylated compounds. Thus, the reaction of (**7-3**) with sodium hydroxide can be visualized as involving first the addition of hydroxide to give a carbinolamine such as (**9-1**) analogous to the methyl amine adduct (**7-4**); a ring opening then will give a chloroacetamide that will cyclize to the observed product (**9-2**). Reaction of that compound with acetic anhydride leads to the formation of acetate (**9-3**) via the typical *N*-oxide Polonovsky rearrangement. Saponification with mild base then gives **oxazepam** (**9-4**) [11].

The alternate strategy used for preparing a hydroxylated derivative from a dichloro analogue relies on the use of a carbethoxy group at the 3 position for activation. The first step consists of condensing diethyl 2-aminomalonate with aminobenzophenone (**10-1**). The reaction probably follows a course similar to that using ethyl glycinate to form an amide such as (**10-2**) as the first intermediate. Exchange of one of the malonate ester groups with the aniline will then lead to the carbethoxy substituted benzodiazepine (**10-3**). Bromination proceeds at the 3 position (**10-4**) that readily enolizes due to the proximity of the two carbonyl groups. Methanolysis of the somewhat labile intermediate replaces the bromine by a methyl ether to give the intermediate (**10-5**). Saponification of the ester group followed by decarboxylation of the β-amidoacid removes the extraneous carbon atom at the 3 position (**10-6**). The methyl ether is then cleaved to an alcohol by means of boron tribromide to afford **lorazepam** (**9-7**) [12].
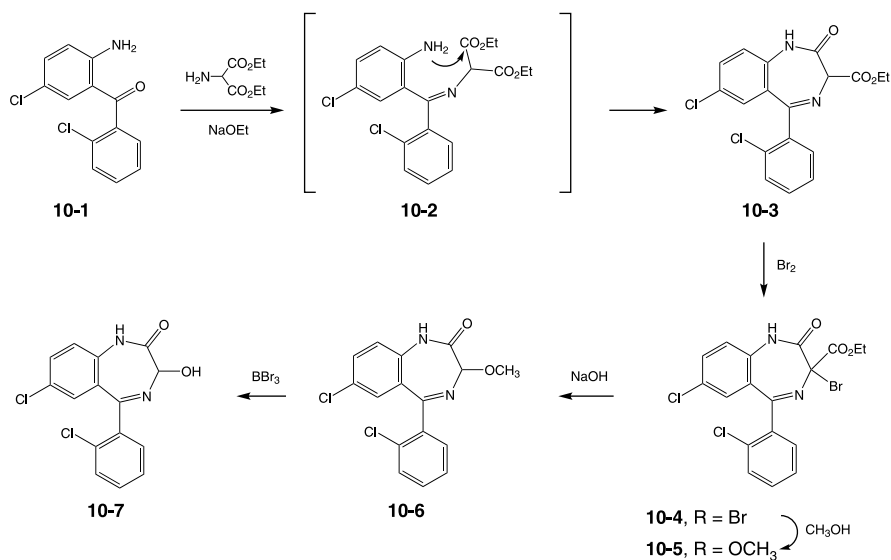
Structure–activity relations in the benzodiazepine series are sufficiently flexible to tolerate a simple tertiary amine rather than an amide carbonyl at the 1 position. An interesting scheme for preparing such compounds relies on an aziridine for supplying the required two-carbon fragment and a subsequent cyclodehydration reaction to form the diazepine ring. The concise sequence starts with the reaction of the anion from *para*-chloro-*N*-methylaniline (**11-1**) with the benzoic acid amide (**11-2**) of aziridine. Opening of the reactive three-membered ring leads the amide (**11-3**) that now contains the requisite atoms for forming the seven-membered ring. Treatment of that amide with phosphorus oxychloride leads to the cyclodehydration and formation of the diazepine ring. There is thus obtained the antianxiety agent **medazepam** (**11-4**) [13].
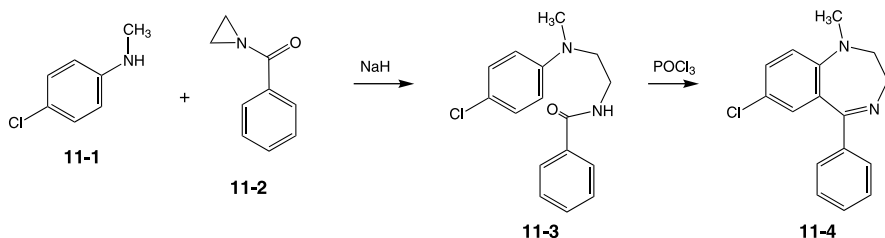
An alternate and equally concise approach to the same compound starts with the reaction of aziridino-benzophenone (**12-1**) with methyl iodide. The outcome of this reaction can be rationalized by assuming the initial formation of quaternary salt (**12-2**). An attack on the strained ring by the iodide counterion will open the ring to afford the *N*-iodoethyl derivative (**12-3**). This then affords **medazepam** (**11-4**) on reaction with HMTA [14].
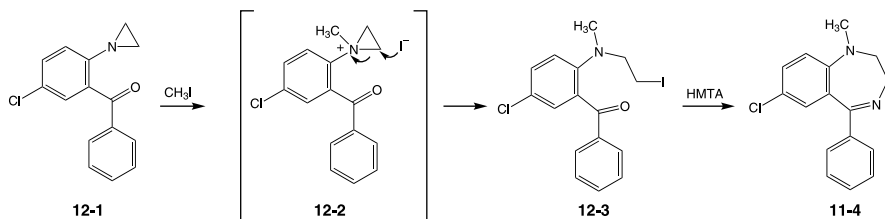
Alkylation of *para*-chloroaniline (**13-1**) with 2,2,2-trifluoroethyl trichloromethyl-sulfonate affords the corresponding trifluroethylated derivative (**13-2**). Reaction of the anion from that with aziridine proper leads to the formation of the diamine (**13-3**). Acylation of that compound with *ortho*-fluorobenzoyl chloride (**13-4**) proceeds to

give the amide (**13-5**). Cyclodehydration of that amide with phosphorus oxychloride gives the benzodiazepine (**13-6**). Ruthenium tetroxide interestingly preferentially oxidizes the 2 position rather than the 3 position adjacent to the imine function. This results in the formation of **fletazepam** (**13-7**) [15].
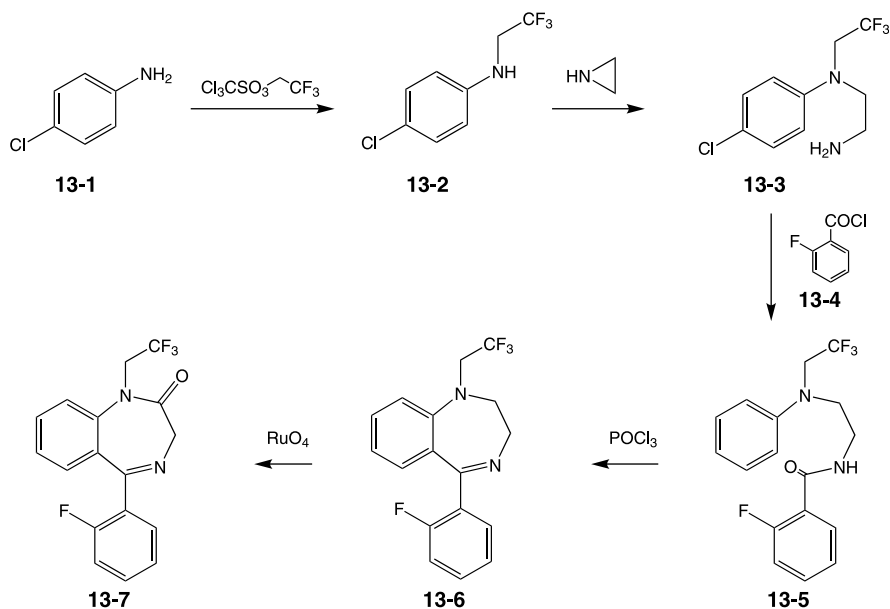
The compound in which nitrogen and carbon at the 4 and 5 positions are transposed and an additional carbonyl group appears at position 2 displays much the same activity as the prototypes. Acylation of the nitrodiphenylamine (**14-1**) with ethyl malonyl chloride gives the corresponding amido-ester (**14-2**). The nitro group is then reduced to the amine by catalytic hydrogenation to give the intermediate (**14-3**). Reaction of that with a strong base closes the benzodiazepine ring (**14-4**). Methylation of the secondary aniline by means of methyl iodide completes the synthesis of **clobazam** (**14-5**) [16].
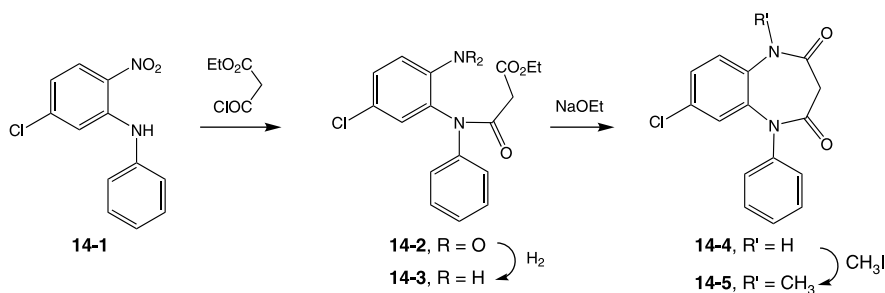
Conversion of an amide a thioamide enhances the reactivity of that function since it favors the enol form and provides a better leaving group for addition-elimination reactions (mercaptide vs. hydroxide). Thioamides obtained by treatment of diazepinone such as (**15-1**) or (**16-1**) with phosphorus pentasulfide provide starting materials for further modification of the benzodiazepine nucleus. (More recently developed reagents such as Lawesson's Reagent or *bis*(tricyclohexyltin) sulfide provide more convenient methods for that transformation.) Thus, reaction of the thioamide (**15-2**) with *O*-allylhydroxylamine leads directly to the amidine, probably via an addition–elimination sequence of the thioenol tautomer of (**15-2**). There is thus obtained the antianxiety agent **uldazapam** (**15-3**) [17].

The thioamide function in addition provides a means for building additional heterocyclic rings onto the basic benzodiazepine nucleus. Many of the products with such additional rings show markedly enhanced potency compared to the simpler compounds discussed so far. This has, not surprisingly, led to the synthesis of hundreds of analogues in the search for agents with unique properties. The reaction of (**15-2**) with acetylhydrazide can be visualized as proceeding through the initial formation of amidine (**15-4**); cyclization with simultaneous bond reorganization will then afford the triazolobenzodiazepine [18]. This product, **triazolam** (**15-5**), is an extremely potent compound that has been used largely as a hypnotic agent because of its apparent short half-life. The drug, under its trade name of Halcion®, has gained considerable notoriety due to reports of bizarre (and unlikely) side effects, including allegations that it induced criminal behavior.
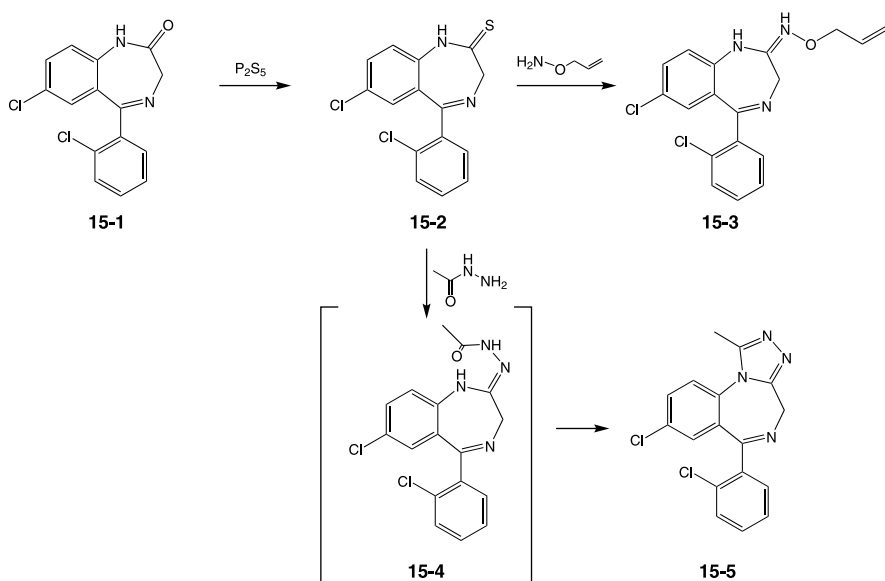
The fused ring can also be built in a stepwise fashion. Reaction of the thioamide (**16-2**) with hydrazine gives the versatile intermediate amidine (**16-3**). Condensation

of that with methyl orthoformate leads to the formation of an unsubstituted fused triazole ring; this affords **estazolam** (**16-4**) [19]. The same reaction using methyl orthoacetate gives the antianxiety agent **alprazolam** (**16-5**) [20].
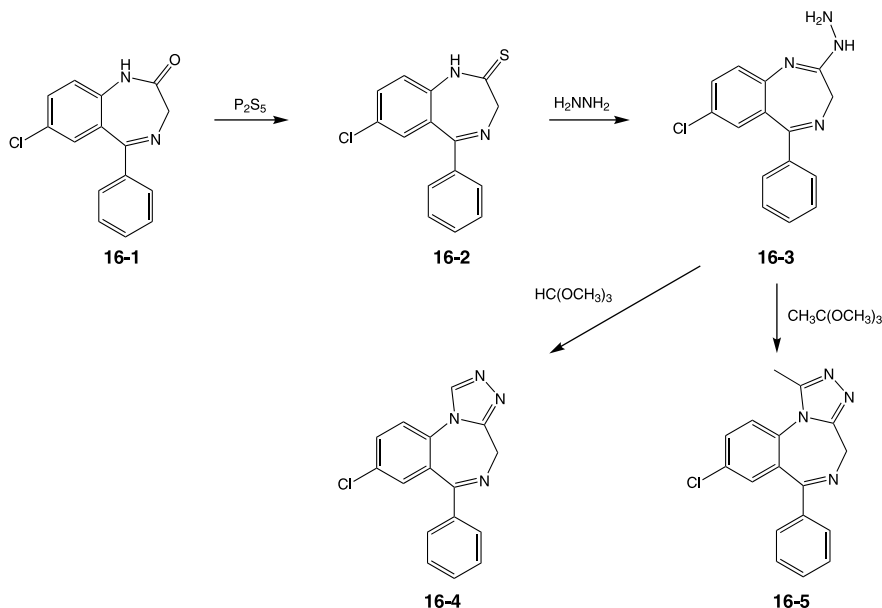
The presence of a basic amino group affords a compound that also shows some degree of antidepressant activity. Acylation of the hydrazine (**16-3**) with chloroacetyl chloride proceeds on the more basic nitrogen to give the hydrazide (**17-1**). Heating that intermediate in acetic acid closes the triazole ring to give the chloromethylated product (**17-2**). The displacement of chlorine by means of dimethylamine then affords **adinazolam** (**17-3**) [21].
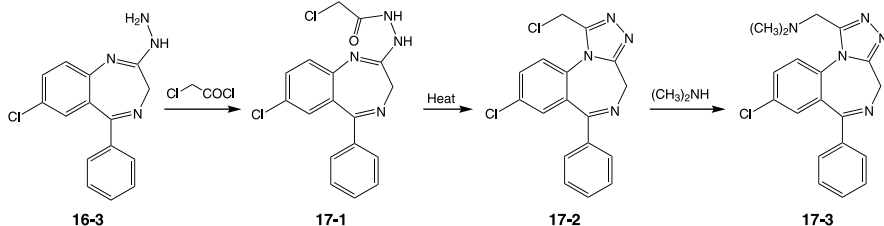
The thioamide function also provides the entry for the construction of a fused imidazole ring, though the sequence is somewhat more complex due to the need to form a new carbon–carbon bond. Reaction of the thioamide (**18-1**) with methylamine proceeds to give the corresponding amidine; this is transformed into a good leaving group by conversion to the *N*-nitroso derivative (**18-2**) by treatment with nitrous

acid. Condensation of that intermediate with the carbanion from nitromethane leads to the displacement of the *N*-nitroso group at the 2 position and the formation of the methyl-nitro derivative; the double bond shifts into conjugation with the nitro group to afford (**18-3**). Treatment with Raney nickel then reduces the nitrovinyl function all the way to an aminomethyl group. Reaction of the resulting diamine (**18-4**) with methyl orthoacetate then leads to the formation of the fused imidazoline ring (**18-5**). Dehydrogenation of that ring with manganese dioxide converts it to an imidazole to give **midazolam** (**18-6**) [22].
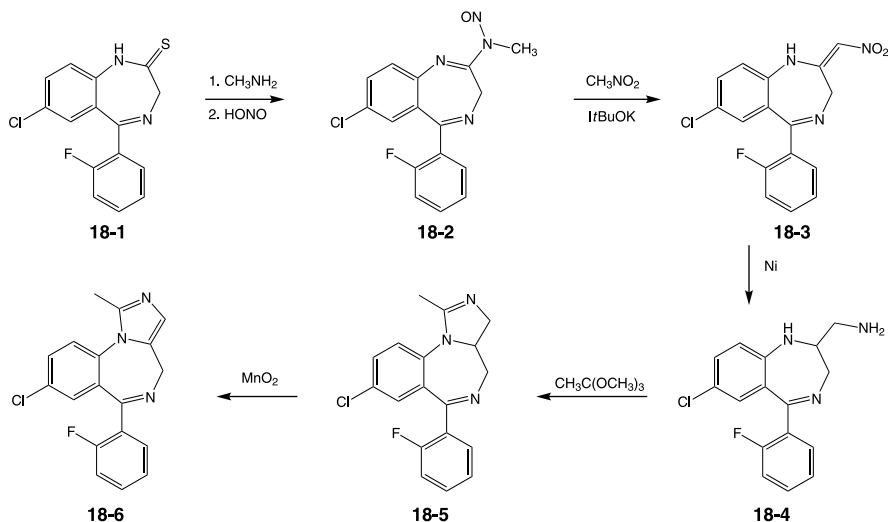
An analogue of these fused benzodiazepines in which the benzene ring at the 5 position is omitted shows benzodiazepine antagonist activity in both *in vitro* binding
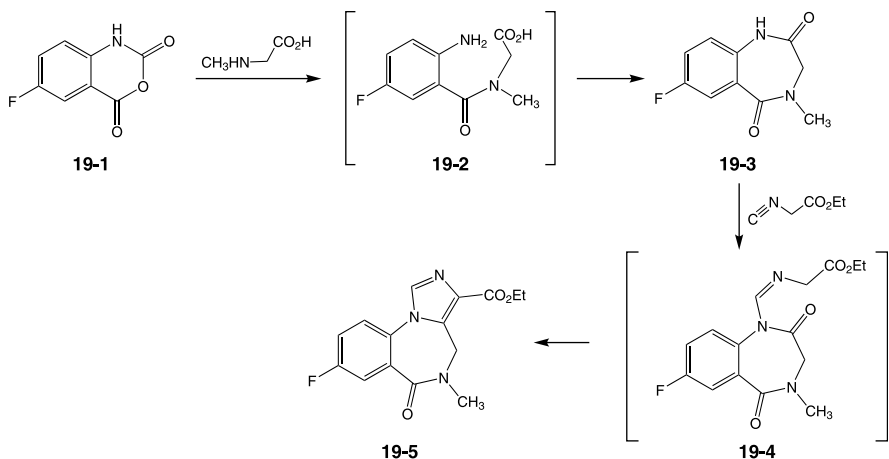
assays and in selected *in vivo* models. The benzodiazepinedione nucleus is obtained from the condensation of the fluorinated isatoic anhydride (**19-1**) with *N*-methylglycine (sarcosine). The first step probably involves the acylation of the amino acid nitrogen by the activated anhydride carbonyl group. The loss of carbon dioxide from the resulting carbamic acid will lead to the amide (**19-2**). This then cyclizes to the benzodiazepinedione (**19-3**). Reaction of this last intermediate with ethyl isocyanoacetate then leads to the addition of the only free amide nitrogen to the isocyanide function to afford an intermediate such as the amidine (**19-3**). The doubly activated acetate methylene group then condenses with the ring carbonyl group to form an imidazole, affording **flumazenil** (**19-5**) [23].

The fusion of an additonal heterocyclic ring onto the above benzodiazepine restores at least partial agonistic activity. The benzodiazepine nucleus is built exactly as above using L-proline (**20-2**) instead of sarcosine to afford (**20-3**). The fused imidazole ring is again added by condensation with an isocyanoacetate, in this case the *tert*-butyl ester. This then affords **bretazenil** (**20-4**) [24], a compound that displays some antianxiety activity.
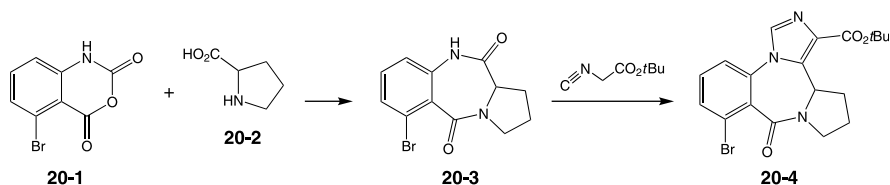
12.2.2. Other Seven-Membered Heterocycles Fused to a Benzene Ring

Peptidomimetic compounds, that is, small molecules that fit receptor sites intended for peptide effectors, are discussed in some detail in Chapter 1. A benzodiazepine provides the backbone for one of the first successful small peptide mimics; that compound, **devapezide** (**21-9**), acts as an antagonist to cholecystokinin, an enzyme with numerous actions including gastric stimulation. The route to this agent uses an alternate to the quinazoline approach for the construction of the required benzodiazepine *N*-oxide. The *N*-oxide function is included as a handle for the eventual introduction of an amino group at the 3 position. Reaction of the product (**21-1**) from the acylation of aminobenzophenone with chloroacetyl chloride with sodium iodide gives the corresponding iodide. Treatment of that intermediate with hydroxylamine leads to the displacement of iodine and the formation of the hydroxylamine (**21-2**). The basic nitrogen then attacks the carbonyl group in a reaction reminiscent of the formation of the pyrimidine ring in **minoxidil** (Chapter 9). This results in the formation of the Schiff base, *N*-oxide (**21-3**). Reaction of the product with acetic anhydride leads to a Polonovski rearrangement. Saponification of the initially formed acetate, (**21-4**) gives the 3-hydroxylated derivative (**21-5**). The newly introduced function is then converted to the chloride by means of thionyl chloride; displacement with

ammonia then gives (**21-6**). Acylation with the acid chloride from indole-2-carboxylic acid (**21-7**) leads to the corresponding amide (**21-8**). Reaction of that product with a strong base leads to the formation of anion on lactam nitrogen; this affords **devapezide** (**21-9**) on treatment with methyl iodide [25].
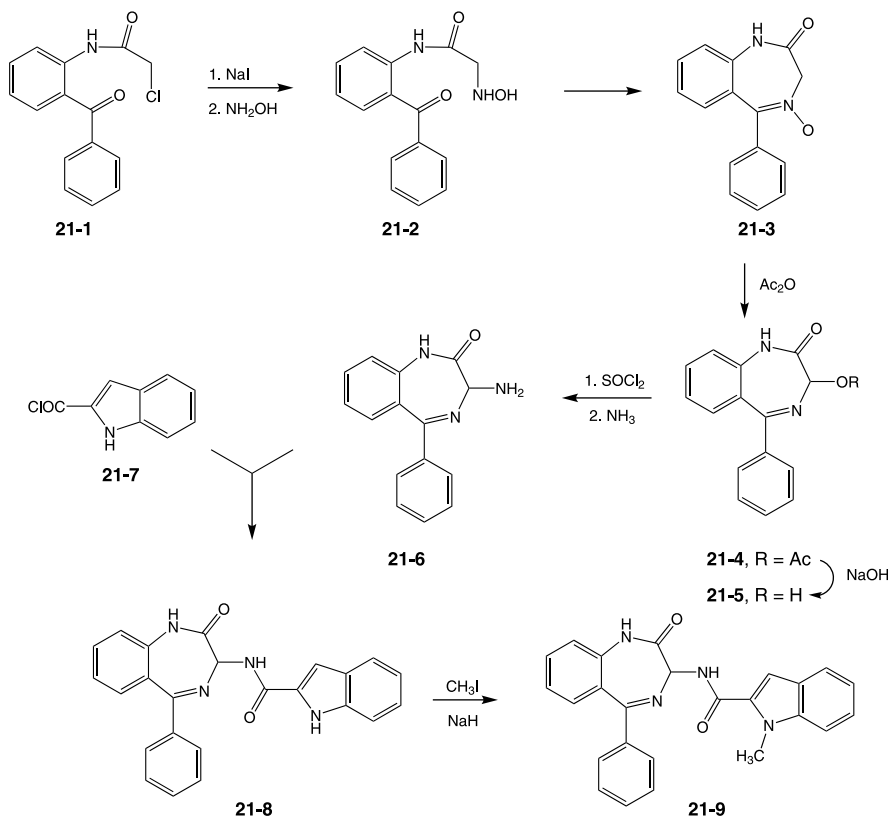
Fused tricyclic compounds have a venerable history as antidepressant drugs. A number of carbocyclic representatives are considered in Chapter 3 while those that consist of dibenzo heterocyclic compounds are noted in Chapter 13. Antidepressant activity is retained in a benzodiazepine in which the third ring occurs in an unfused
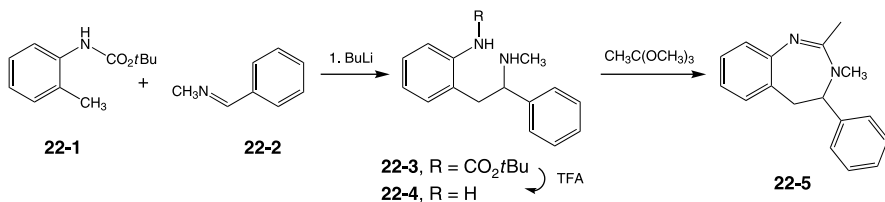
form. The concise synthesis starts with the addition of the carbanion from the toluidine amide (**22-1**) to the Schiff base from benzaldehyde to give the 1,2-diphenyl ethane derivative (**22-3**). The carbobenzoxy protecting group is then removed by means of trifluoroacetic acid. Reaction of the resulting diamine (**22-4**) with methyl orthoacetate adds the required extra carbon atom and leads to the formation of the diazepine **dazepinil** (**22-5**) [26].

A triazole provides the third ring in a tricyclic antidepressant agent that also includes the pendant piperazine ring often found in this class of CNS agents. Reaction of the iminoether (**23-1**) from *ortho*-nitrophenylacetonitrile with acethydrazide leads to the formation of the triazole ring (**23-2**). The nitro group is then reduced to the amine, (**23-3**) by catalytic hydrogenation. Treatment of this compound with carbonyl diimidzole (CDI) bridges the aniline and triazole functions to afford the urea (**23-4**). This is converted to the enol chloride (**23-5**) by the standard phosphorus oxychloride reaction. The displacement of halogen by means of *N*-methylpiperazine leads to the formation of **batelapine** (**23-6**) [27].
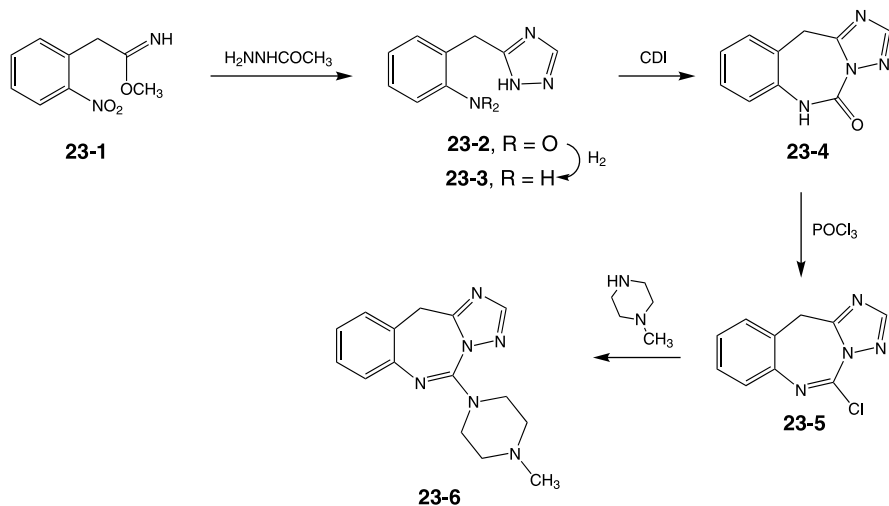
The synthesis of a compound in which the piperazine is incorporated in the form of an additional fused ring starts with the condensation of 2-nitrobenzylamine (**24-1**) with 2,5-dimethoxy tetrahydrofuran (**24-2**). This latent 1,5-dialdehyde reacts with the primary amino group to form the benzylpyrrole (**24-3**). The nitro group is then reduced catalytically to give the aniline (**24-4**). An acid-catalyzed reaction of that intermediate with the hemicetal from ethyl glyoxal leads to the tricyclic nucleus (**24-5**). That reaction can be visualized as involving an initial addition of aniline to the aldehyde to form a protonated imonium ion, which then attacks the pyrrole to form the central ring. Acylation of the intermediate with chloroacetyl chloride then gives chloromethyl amide (**24-6**). Treatment of this last product with methylamine leads to the amide (**23-7**) by the intial displacement of chorine followed by

ester-amide interchange. Reaction with lithium aluminum hydride then leads to the reduction of both amide groups and thus the formation of the antidepressant agent **aptazepine** (**24-8**) [28].
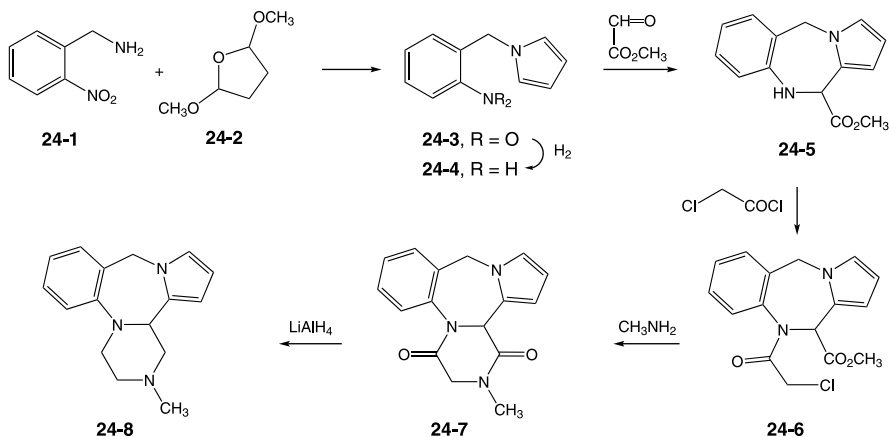
The pituitary hormone arginine vasopressin (AVP) plays a pivotal role in regulating blood volume. Broadly speaking, excessive release of the hormone will cause the kidneys to reabsorb water and thus increase blood volume. An AVP antagonist would thus be useful in treating disease marked by excessive water retention such as, most notably, congestive heart failure. A pyrrolobenzazepine forms an important part of a nonpeptide AVP antagonist. Acylation of the known pyrrolobenzazepine (**25-1**) with the nitrobenzoyl chloride (**25-2**) proceeds in a straightforward fashion to the amide (**25-3**). Reduction of the nitro group by means of hydrogenation or stannous chloride affords the corresponding aniline (**25-4**). Acylation of the newly formed amino group with the benzoyl chloride (**25-5**) then affords **lixivaptan** (**25-6**) [29].
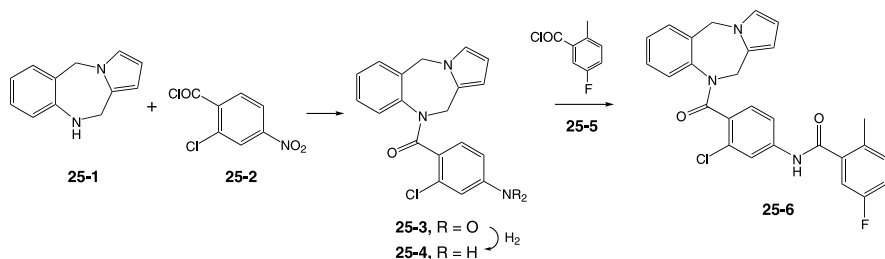
Yet a further variation of this theme consists in the replacement of the bridging methylene group by sulfur to give a thiadiazepine as the central ring. The starting thiophene ether (**26-3**) is obtained by the nucleophilic aromatic displacement of fluorine in nitrobenzene (**26-1**) by the anion from imidazole-2-thiol (**26-2**). The nitro

group is then reduced to the aniline (**26-4**). The amine groups are bridged much as above, though in this instance by use of thiophosgene to give the thiadiazepine (**26-5**). Alkylation of the thioamide with methyl iodide locks that function into its enol form (**26-6**) and at the same time converts sulfur to the potential good leaving group, methyl mercaptan. Reaction of that product with *N*-methylpiperazine thus results in the formation of the displacement product, **pentiapine** (**26-7**) [30].
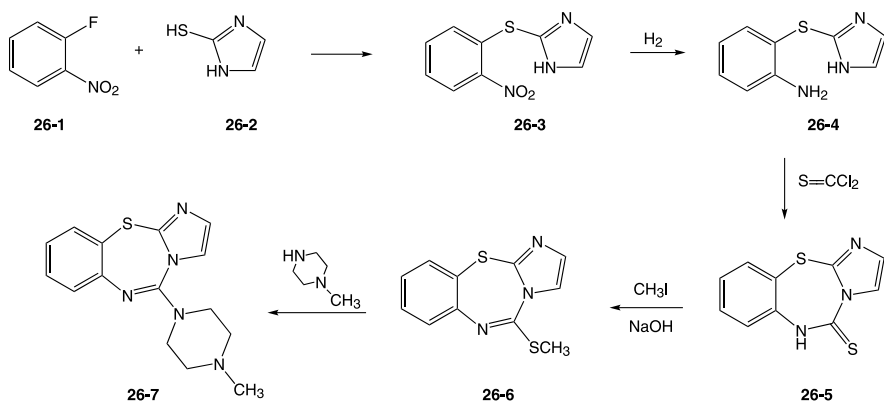
A benzoazathiazepine provides the nucleus for a structurally unusual calcium channel blocker. This was, incidentally, one of the first of the growing class of drugs provided as the pure biologically active enantiomer. The key, and very carefully studied, reaction to the preparation of this compound consists of the opening of the racemic glycidic ester (**27-2**) with nitrothiophenol (**27-1**). The reaction proceeds to
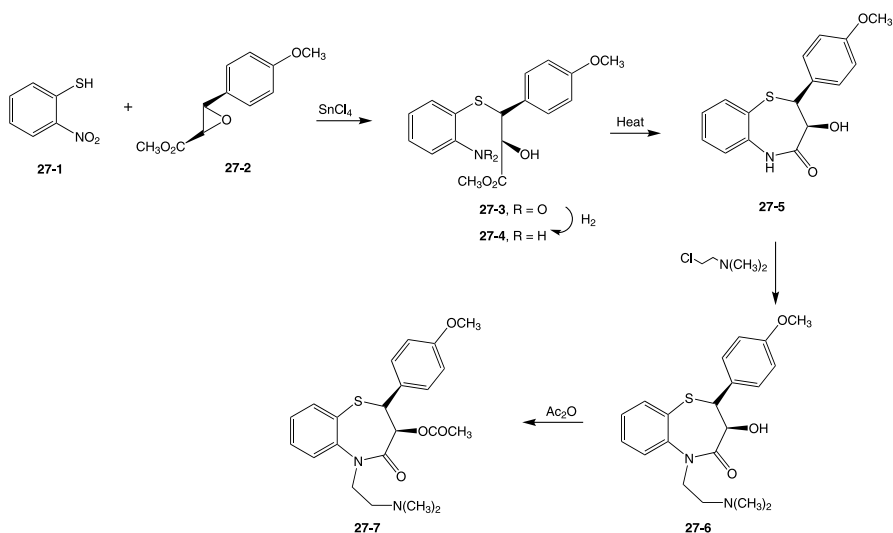
give the *threo* hydroxyester; tin salt catalysis ensures the unusual highly specific *cis* opening of the oxirane ring. The product is then saponified to its acid and that resolved as its cinchonine salt. The sequence then proceeds with the re-esterified isomer whose absolute configuration corresponds to (**27-3**). The nitro group is next converted to the amine by catalytic hydrogenation; heating the product closes the amide ring to give (**27-5**). The requisite side chain is then added by alkylation of that product with 2-chloroethyldimethylamine (**27-6**). Acetylation of the free hydroxyl group with acetic anhydride completes the synthesis of **diltiazem** (**27-7**) [31].

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CHAPTER 13

HETEROCYCLES FUSED TO TWO AROMATIC RINGS

13.1. COMPOUNDS CONTAINING A SINGLE HETEROATOM

13.1.1. Derivatives of Dibenzopyran and Dibenzoxepin

Anticholinergic agents comprised one of the very few drugs available for the treatment of gastric ulcers prior to the advent of the highly specific H_2 antihistamine gastric acid secretion inhibitors or the subsequent drugs that act by interfering with the action of cellular sodium potassium pumps. The earlier anticholinergic agents were often converted to characteristically poorly absorbed quaternary salts in order to hopefully confine the compounds to the desired site of action in the GI tract. The starting phenoxybenzoic acid (**1-1**) for one of these agents can be obtained by the nucleophilic aromatic displacement of halogen from 2-chlorobenzoic acid. Friedel–Crafts cyclization using, for example, concentrated sulfuric acid leads to the dibenzopyranone (**1-2**). Treatment of that compound with sodium in ethanol leads initially to a benzhydrol; that very labile hydroxyl is then reduced further to give the parent dihydrodibenzopyran (**1-3**). Reaction of the anion from that intermediate with carbon dioxide gives the acid (**1-4**) on acidification. The carboxylate salt from that intermediate is then alkylated with 2-chlorotriethylamine to afford the corresponding ester; reaction of this product with bromomethane leads to the quaternary methobromide and thus **methantheline bromide** (**1-5**) [1].
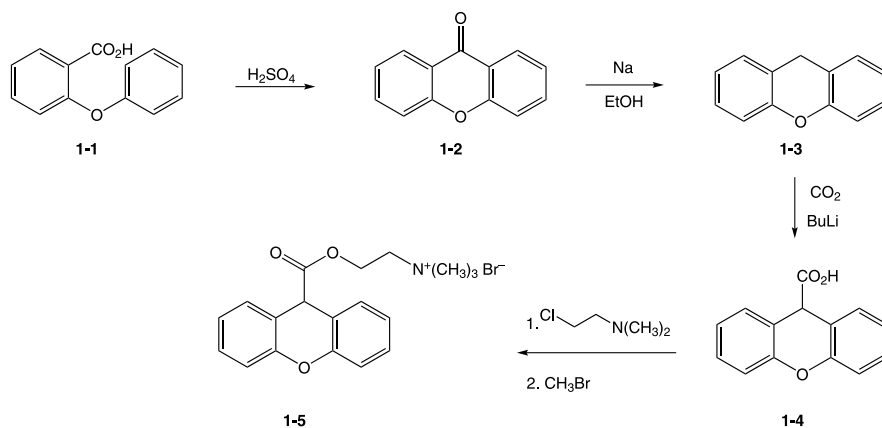
The dibenzopyranone ring system may be viewed as a chromone with an additional fused benzene ring and thus generally related to the antiasthmatic mediator release inhibitor **cromolyn** (see Chapter 11). Two dibenzopyranones have in fact been investigated for this indication in the clinic. Friedel–Crafts cyclization of the substituted cresyloxybenzoic acid (**2-1**) in sulfuric acid leads to the dibenzopyranone (**2-2**). The methyl group is then oxidized to a carboxylic acid by means of chromic acid. The acid is then converted to its sodium salt, **xanoxate sodium** (**2-3**) [2].
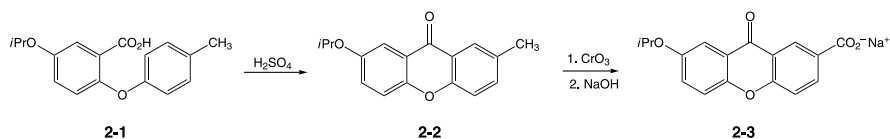
The preparation of the analogue in which a sulfoxide group replaces the isopropyl ether involves a more complex scheme. The starting bromobenzoate (**3-2**) in this case includes a pre-formed carboxyl group. The replacement of halogen in this compound by the alkoxide from hydroquinone monomethyl ether (**3-1**) leads to the diphenyl ether (**3-2**). The dibenzopyranone (**3-5**) is obtained by Friedel–Crafts cyclization of the saponification product (**3-4**) from (**3-3**). The methyl ether in that intermediate is cleaved with hydrogen bromide and the carboxylic acid (**3-6**) is re-converted to an ester to afford (**3-7**). The phenol is then converted to the corresponding thiophenol by an interesting oxygen–sulfur interchange reaction sequence [3]. The first step in this interchange comprises the conversion of the phenol to the thiocarbamate (**3-8**) by reaction with N,N-dimethylthiocarbamoyl chloride. On heating, this intermediate undergoes oxygen to sulfur migration to give the isomeric thiocarbamate (**3-9**), with a consequent exchange of the phenol oxygen with sulfur. Treatment of the rearrangement product with an aqueous base leads to the saponification of both the thiocarbamate and ester groups to afford the free thiophenol (**3-10**). This is converted

to the corresponding methyl ether (**3-11**) by means of methyl iodide. The oxidation of sulfur in this last intermediate with periodic acid then affords the mediator release inhibitor **tixanox** (**3-12**) [4].
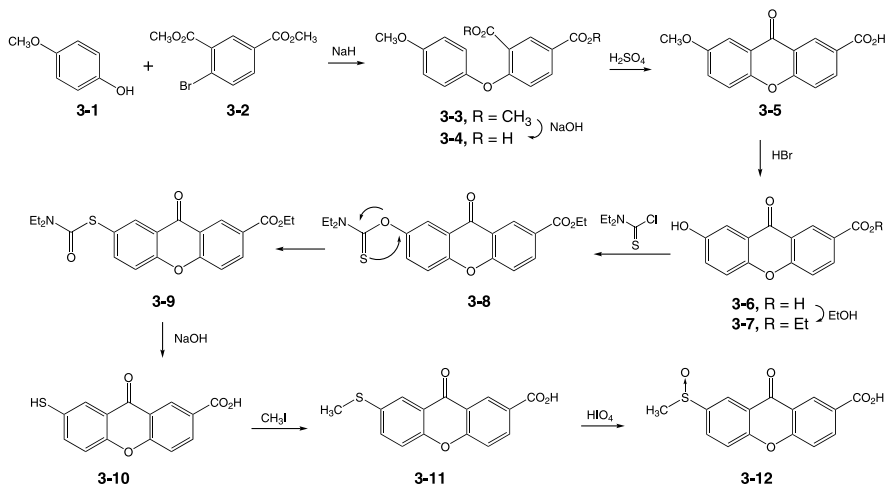
Tricyclic antidepressant drugs often show nonspecific analgesic activity that is unrelated mechanistically to that manifested by either opioids or NSAIDs. The dibenzoxepin **fluradoline** (**4-5**), which is structurally related to the antidepressants discussed later in this chapter, is used as an analgesic as well as a psychotropic agent. Hydrolysis of the cyano group in the starting nitrile (**4-1**) with sulfuric acid followed by treatment of the resulting acid with thionyl chloride affords the acid chloride (**4-2**). This cyclizes to the dibenzoxepinone (**4-3**) on treatment with aluminum chloride. The carbonyl group in that product readily converts to its enol form due to stabilization from conjugation of the resulting double bond with both adjacent aromatic rings.
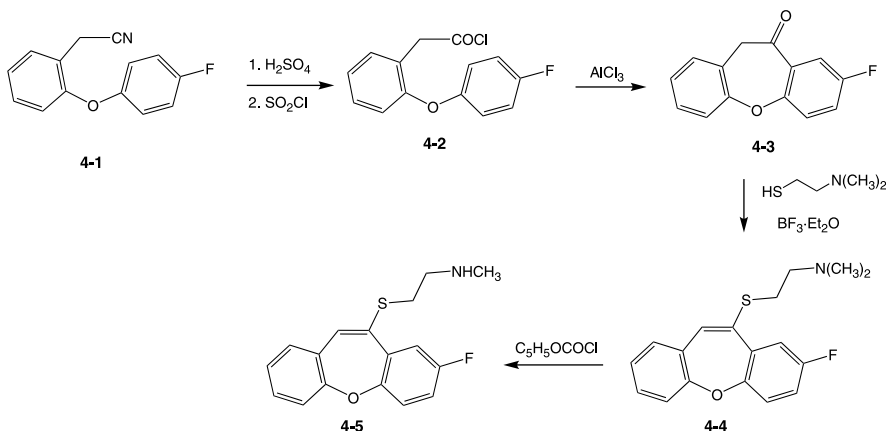
Thus, reaction of (**4-3**) with *N,N*-dimethylthioethanolamine leads to the incorporation of the basic side chain in (**4-4**) via a thioenol ether linkage. One of the methyl groups on nitrogen is then removed by reaction with phenyl chloroformate in the modern version of the von Braun reaction to afford **fluradoline** (**4-5**) [5].

The nucleus for the prototype tricyclic antidepressant **imipramine** (**17-5**), discussed in the next section, consists of a dibenzazepine system. That activity is retained when the nucleus is replaced by a dibenzoxepin. The propylamino side chain in this compound is attached to a trigonal sp^2 carbon rather than a trigonal nitrogen. Nucleophilic displacement provides the key to entry to the required isomeric dibenzoxepinone (**5-5**). Thus, the replacement of halogen in the benzyl bromide (**5-2**) by phenoxide leads to the corresponding phenyl ether (**5-3**). Saponification then leads to the free acid (**5-4**). Friedel–Crafts cyclization of this acid in hot polyphosphoric acid then leads to the dibenzoxepinone (**5-5**). Condensation of that intermediate with the Grignard reagent from 3-chloro-1-(*N,N*-dimethylamino)propane leads initially to the tertiary carbinol (**5-6**). This dehydrates spontaneously on workup to give the olefin that consists primarily of the E isomer [5]. The stereoselectivity may result from the fact that (**5-6**) is actually puckered; the isomer from a preferential addition to the ketone from the face of the molecule containing oxygen can form a hydrogen bonded bicyclic intermediate that will favor the formation of the *trans* isomer on dehydration. As used for drugs, **doxepin** (**5-7**) consists of a 5 : 1 mixture of E and Z isomers [6].
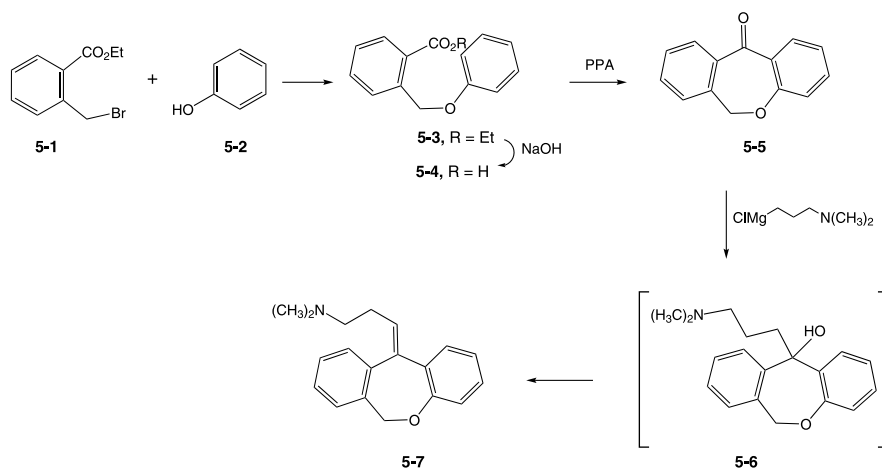
The displacement of bromine from (**5-1**) with the phenoxide from *meta*-hydroxyphenylacetic acid (**6-1**) gives the phenyl ether (**6-2**). Saponification then leads to the dibasic acid (**6-3**). Ring closure of this compound with polyphosphoric acid gives the dibenzoxepinone. This product, **isoxepac** (**6-4**), not unexpectedly, displays NSAID activity [7].
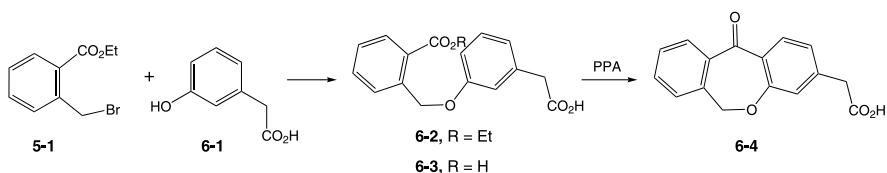
A dibenzoxepin with an acetic acid residue at an alternate position provides the starting material for an H$_1$ antiallergy antihitsamine. The presence of the polar carboxylic acid function presumably keeps the drug from penetrating the blood-brain barrier, avoiding CNS-mediated side effects. The starting dibenzoxepin (**7-2**) is presumably available from a scheme analogous to that used for isoxepac, starting instead with *para*-hydroxyphenylacetic acid (**7-1**). Condensation of (**7-2**) with the ylide from triphenyl-3-dimethylaminopropylphosphonium bromide then adds the basic side chain. The product, **olopatadine** (**7-3**), is obtained as a 7:3 mixture of the Z and E isomers [8].
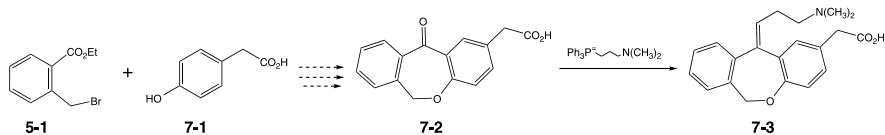
The potential antipsychotic drug **asenapine**, which consists of a dibenzoxapine, was actually first described in a 1979 patent [9]. The compound was revived presumably because data obtained on this agent using more recent pharmacological methods showed an unusual pattern of binding to various CNS receptor types. Condensation of the acid chloride (**8-1**) with *N*-methylglycine ethyl ester leads to the amide (**8-2**). Treatment of that intermediate (**8-2**) with potassium *tert* butoxide leads the enolate adjacent to the aromatic ring to add to the ester at the end of the side chain, thus forming the pyrrolidine ring (**8-3 = 8-4**). Heating that intermediate in polyphosphoric
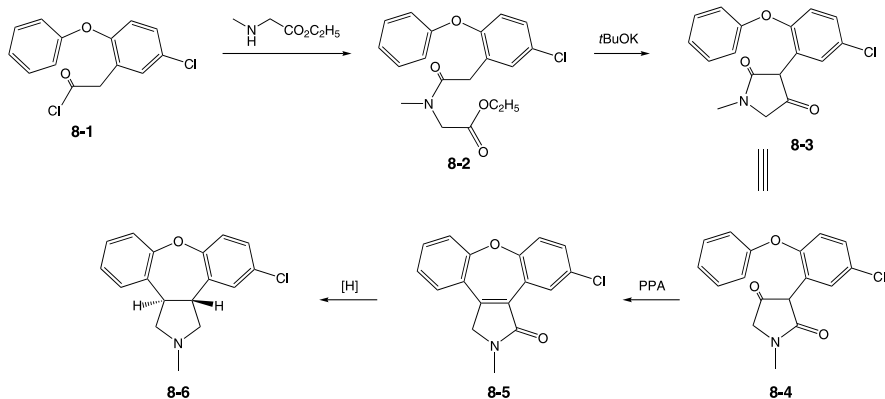
acid leads to a reaction of the ketone carbonyl group with the other aromatic ring to form the benzoxazine (**8-5**). The unsaturation in the seven-membered ring is then reduced by means of sodium in liquid ammonia, leading to the product with a *trans* ring junction. The amide function is then taken on the amine by means of a metal hydride. Resolution, not described in the patent, will then afford chiral asenapine (**8-6**).

13.1.2. Dibenzo Heterocycles Containing One Ring Nitrogen Atom

The standard dopamine-blocking antiemetic agents are of little avail for treating the often debilitating nausea and emesis caused by the administration of many cancer chemotherapy agents. The discovery of the serotonin antagonists such as **ondansetron** (**9-6**) has provided a means for controlling this treatment-limiting side effect. The starting material, (**9-4**) for this drug can be obtained by alkylation with methyl iodide of the partly reduced carbazole (**9-3**) from the Fischer indole condensation of dihydroresorcinol (**9-2**) and phenylhydrazine. Mannich reaction of the product with formaldehyde and dimethylamine gives the aminomethylated derivative (**9-5**). Treatment of the intermediate with 2-methylimidazole leads to the replacement of dimethylamine by the heterocycle, either by direct SN_2 displacement or, alternatively, by elimination to the exomethylene derivative followed by conjugate addition of the imidazole. There is thus obtained **ondansetron** (**9-6**) [10].
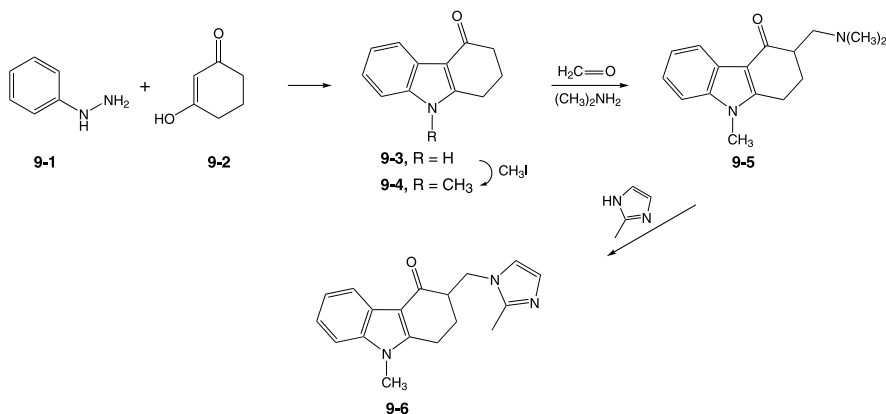
Antiemetic activity is retained when the point of attachment of the imidazole ring is changed from nitrogen to carbon. Thus, aldol condensation of trityl-protected imidazole aldehyde (**10-1**) and carbazole (**9-4**) leads to the carbinol (**10-2**). Treatment of that intermediate with toluenesufonyl chloride affords the corresponding tosylate; this eliminates to form the olefin (**10-3**) on treatment with a base. The double bond is then reduced by catalytic hydrogenation; a strong acid then removes the trityl protecting group. Resolution of this last product by means of salt formation then affords **galdansetron** (**10-4**) [11].
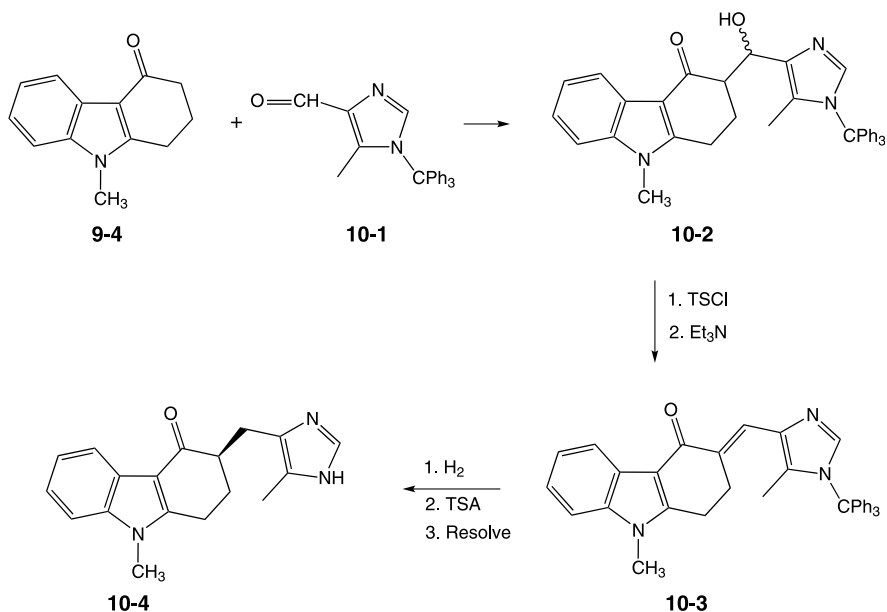
The great majority of antimalarial agents, as noted in Chapter 11, consist of substituted quinolines. It is an interesting circumstance that the drug that has been most widely used as a prophylactic and curative antimalarial is in fact an acridine. This agent, **quinacrine** (**11-7**), better known to veterans of World War II as Atabrine, became available just before that war and was widely used by armies on both sides in tropical areas. The first step in the synthesis of this agent consists of nucleophilic aromatic displacement of chlorine from 2,4-dichlorobenzoic acid (**11-1**) to give the diphenylamine (**11-3**). Treatment of the product with phosphorus oxychloride proceeds initially to the acridone (**11-4**). Excess reagent then converts what is in effect a vinylogous amide to its enol chloride (**11-5**), going to the aromatic heterocycle
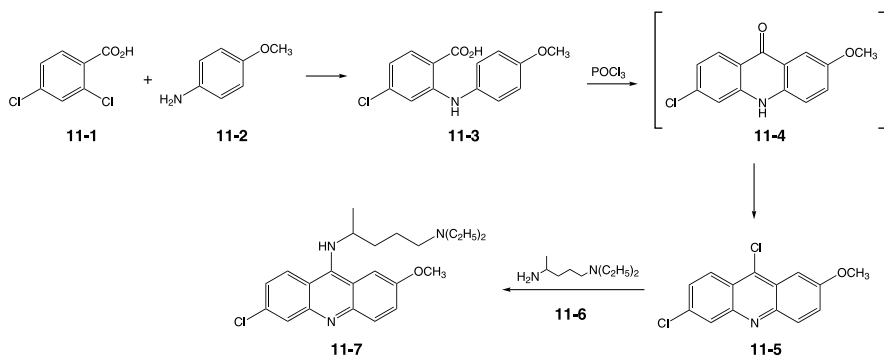
in the process. The displacement of chlorine with 4-amino-5-(dimethylamino)pentane (**11-6**) then gives **quinacrine** (**11-7**) [12].

The fact that the ketone in acridones undergoes normal Grignard reactions indicates that it retains considerable carbonyl character. Thus condensation of the acridone (**12-1**) with the organomagnesium derivative from 3-(dimethylamino)choloropropane gives the corresponding tertiary carbinol on workup; this readily dehydrates to the olefin (**12-2**) on heating. Note that this compound can readily tautomerize to the aromatic acridine. Catalytic hydrogenation then gives the dihydroacridine, **clomacran** (**12-3**) [13]; this compound shows the same type of antipsychotic activity as the better-known phenothiazines discussed below.
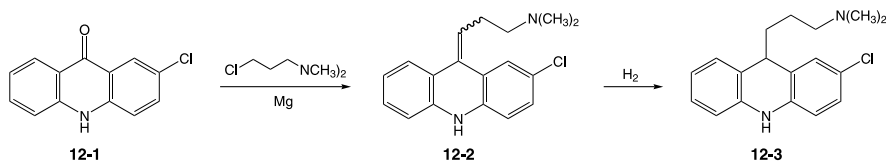
Reaction of diphenylamine (**13-1**) with acetone in a strong acid leads to the formation of the acridan addition product (**13-2**). The reaction can be envisaged as involving an initial formation of a hydrated carbocation such as $Me_2C\text{-}OH^+$; this attacks one of the aniline rings to give the corresponding tertiary carbinol; that then undergoes normal cyclodehydration to give the observed product (**13-2**). Alkylation of that intermediate with 3-(dimethylamino)choloropropane then gives **dimetacrine** (**13-3**) [14]; this compound, which may be viewed as a ring contracted analogue of **imipramine** (**17-5**), shows similar antidepressant activity.
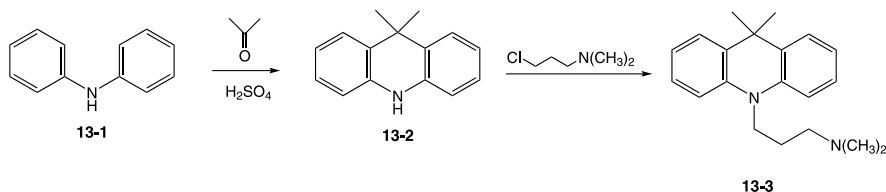
The devastating mental deterioration that characterizes Alzheimer's disease has been attributed to a mishandling of the neurotransmitter acetylcholine. Inhibitors of acetylcholinesterase, the enzyme that catabolizes that substance, would be expected to help restore deficient acetylcholine levels. Several partly reduced acridines have shown some activity in treating Alzheimer's disease. At least one of these, **tacrine** (**14-5**), is now approved for use in patients. The initial step in the synthesis of the first of these consists of the sodium amide catalyzed condensation of isatin (**14-1**) with cyclohexanone. The reaction can be visualized by assuming the first step to involve an attack of amide on isatin to give an amido-amide such as (**14-2**) (note that no attempt has been made to account for charges). This can then react with

cyclohexanone to lead to the enamine (**14-3**). Normal enamine chemistry will then give the observed product, acridine carboxamide (**14-4**). That intermediate is then subjected to Hoffmann degradation; treatment with bromine in the presence of sodium hydroxide leads to **tacrine** (**14-5**) [15].
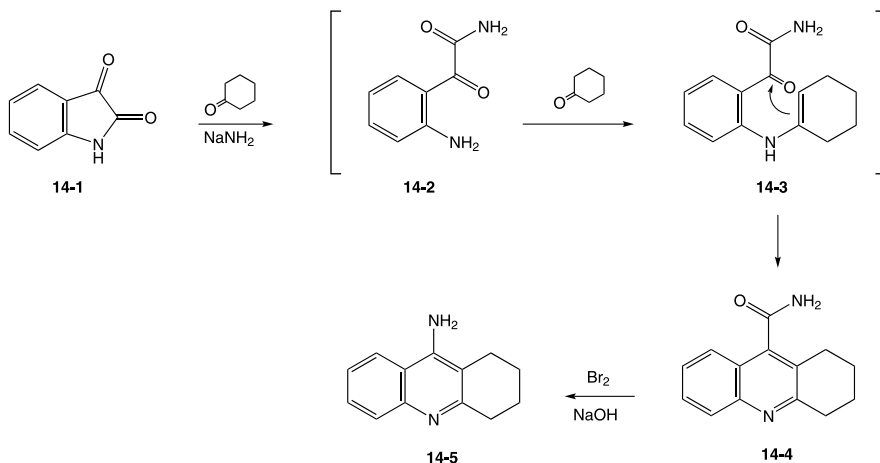
The inclusion of a hydroxyl group increases the hydrophilicity of the compound and presumably also improves the oral absorption over that of the very hydrophobic parent drug. In a conceptually related synthesis, *ortho*-aminobenzonitrile (**15-1**) is condensed with dihydroresorcinol to give the isolable enamine (**15-2**). Treatment of that intermediate with the Lewis acid cuprous chloride leads to the addition of the enamine to the nitrile to yield an addition product such as (**15-3**). That intermediate then tautomerizes to give the fully conjugated dihydroacridine (**15-4**). The carbonyl group is then reduced with lithium aluminum hydride to afford **velnacrine** (**15-5**) [16].
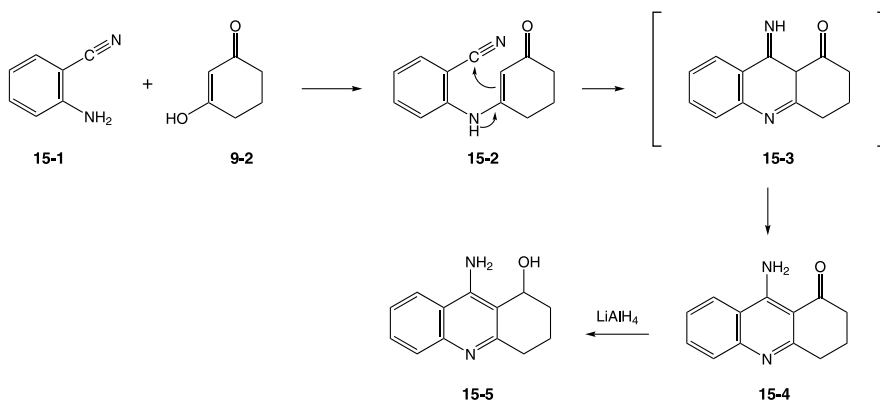
The nitrogen mustards, compounds that incorporate a *bis*-chloroethylamino moiety, have a venerable history as cytotoxic agents used in cancer chemotherapy.

The indiscriminate killing action of alkylating agents is not restricted to eukaryotic cells; the compounds also inactivate microbes. A recent nitrogen mustard–containing compound is now proposed for use *ex vivo* to inactivate pathogens in blood transfusion supplies. The acridine portion of **amustaline** (**16-6**) is intended to intercalate in DNA, a well-known property of this structural element, and thus bring the mustard to the intended site of action. Excess drug that is not complexed can be expected to be destroyed by blood enzymes or even by simple hydrolysis. This should minimize exposure by patients who receive treated blood to unreacted mustard. Construction of this agent starts by displacement of chlorine from 9-chloroacrdine (**16-1**) by the terminal amine on a so-called β-alanine ester (**16-2**) in the presence of sodium methoxide. Saponification then yields the corresponding acid (**16-3**). Esterification of the carboxyl group with triethanolamine (**16-4**) leads to the ester (**16-5**). The free hydroxyl groups on this intermediate are then replaced by chlorine by reaction with thionyl chloride. There is thus obtained **amustaline** (**16-6**) [17].
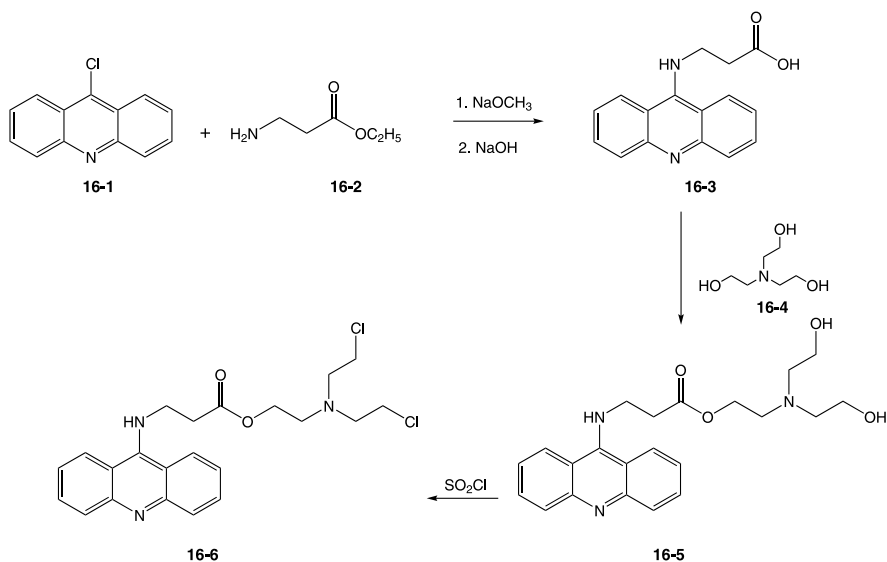
The prototype for the large class of tricyclic antidepressant compounds, **imipramine** (**17-5**), can be viewed as a bioisostere of a phenothiazine in which an ethylene bridge replaces the central ring sulfur in the latter. Anecdotal evidence suggests that the actual activity of this drug was uncovered serendipetously while it was in trial as an antipsychotic agent. One of the early syntheses for this dibenzazepine starts with the self-alkylation of *ortho*-nitrobenzyl chloride. The first step consists in the displacement of halogen from (**17-1**) by an anion from the reaction of a second equivalent to form the transient intermediate (**17-2**). The elimination of hydrogen chloride then leads to the stilbene (**17-3**) as a mixture of isomers. Catalytic hydrogenation then reduces both the nitro groups and the double bond to afford diamine (**17-4**). Pyrolysis of that compound leads to the formation of the dibenzazepine

ring (**17-4**) by an unusual nucleophilic aromatic displacement reaction. The anion from the treatment of (**17-4**) with sodium amide is then treated with 3-chloro-1-dimethylaminopropane to afford **imipramine** (**17-5**) [18]. The metabolite, **desipramine** (**17-6**), has the same activity as the parent. This observation is repeated for the majority of antidepressant compounds. This makes it difficult to identify the proximate active species. These mono-methyl derivatives are obtained by the von Braun demethylation reaction or one of its modern equivalents.
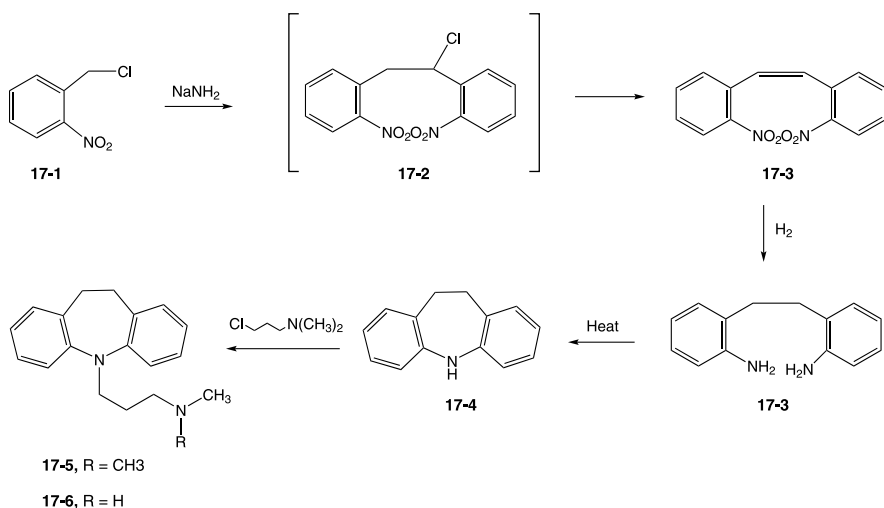
Ring expansion of more readily accessible acridines provides an alternate method for preparing the dibenzazepines. The starting halide (**18-1**) can be obtained by chlorination of the corresponding *N*-acetyl dihydroacridine. The displacement of
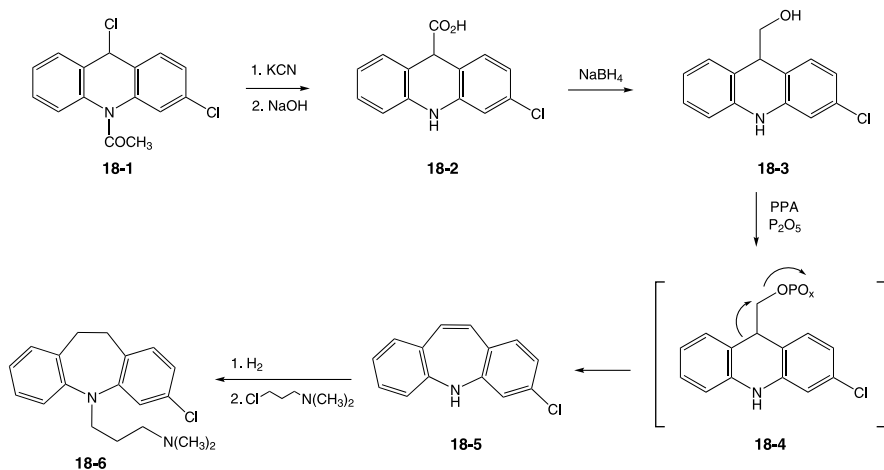
chlorine by cyanide gives the nitrile; this is then hydrolyzed to the acid with a base. The amine is deacylated under the reaction conditions to afford (**18-2**). The carboxyl group is next reduced to the carbinol by means of sodium borohydride to give the intermediate (**18-3**). Reaction of that with polyphosphoric acid and phosphorus pentoxide probably leads initially to the formation of phosphates esters such as (**18-4**). These transient intermediates then rearrange in a concerted manner or via a discreet carbocation to afford the ring enlarged product (**18-5**). The double bond is then reduced by catalytic hydrogenation. Alkylation on nitrogen as above leads to the antidepressant **chlorimipramine** (**18-6**) [19].

The reaction of dibenzazepine (**17-4**) with acetic anhydride gives the corresponding protected intermediate. Treatment of that with *N*-bromosuccimide leads to bromination at the benzylic position to give (**19-1**). This is then dehydrohalogenated by means of collidine to afford the dehydro derivative (**19-2**). The protecting group is next removed by basic hydrolysis (**19-3**). The resulting amine is then converted to the carbamoyl chloride with phosgene; exposure of that reactive intermediate with ammonia gives the corresponding urea [20]. This product, **carbamazepine** (**19-4**), is a widely used anticonvulsant agent.
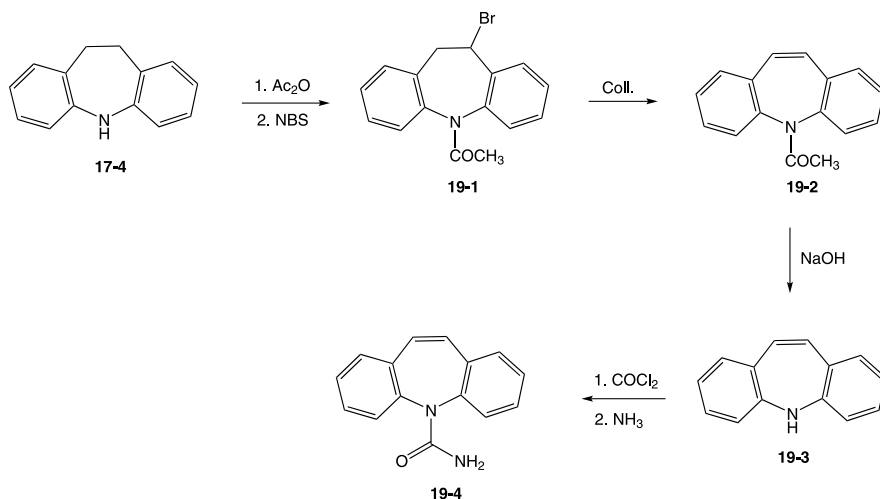
Many of the tricyclcic antidepressants show some measure of undesired anticholinergic activity that may provoke side effects such as dry mouth and increased heart rate. Anticholinergic activity predominates in a dibenzazepine in which nitrogen is moved to the two-atom bridge. Condensation of anthraquinone (**20-1**) with the Grignard reagent from 3-chloro-1-dimethylaminopropane, in the cold, leads to the mono-adduct (**20-2**); steric hindrance about the remaining carbonyl group may account for this selectivity. The ketone is then converted to its oxime (**20-3**) by means of hydroxylamine. Treatment of this intermediate with a mixture of phosphorus pentoxide and polyphosphoric acid results in the formation of the ring enlarged lactam by a classic Beckmann rearrangement; the labile tertiary benzhydryl alcohol dehydrates under these reaction conditions to give (**20-4**) as a mixture

of isomers. The lactam is then reduced to the secondary amine (**20-5**) by means of lithium aluminum hydride. Base-catalyzed alkylation with methyl iodide then affords **elantrine** (**20-6**) [21].
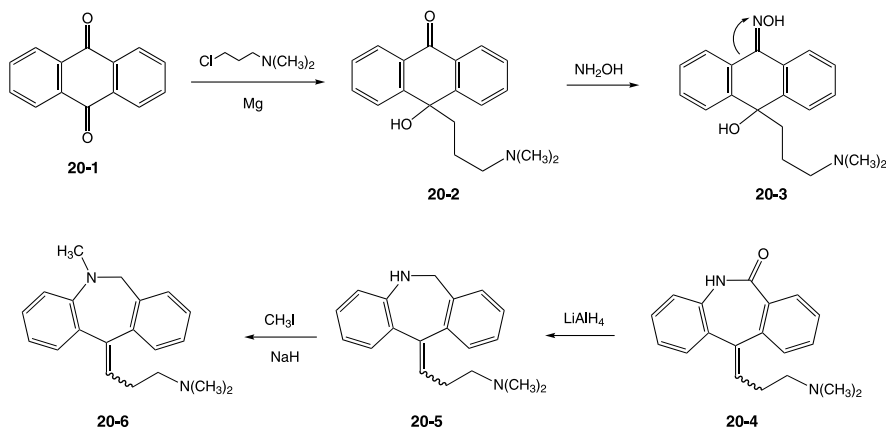
13.1.3. Dibenzo Heterocycles with One Sulfur Atom

The thioxanthone ring system comprises the nucleus for two of the more efficacious orally active antischitosomal drugs. One synthesis for these compounds starts with the chlorsulfonation of *para*-chlorotoluene (**21-1**) to give the sulfonyl chloride (**21-2**). Treatment of the product with zinc in aqueous sulfuric acid leads to a reduction of the sulfonyl chloride to form the thiophenol (**21-3**). The key to the formation of this and related thioxanthones and xanthenes consists of the Ullman reaction, which
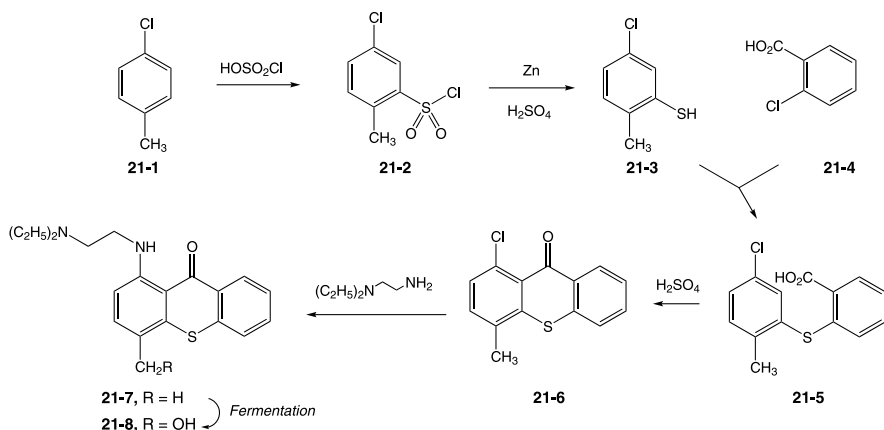
involves copper-catalyzed displacement of aromatic halogen by sulfur. Condensation of *ortho*-chlorobenzoic acid with (**21-4**) under Ullman conditions thus affords the *bis*-aryl thioether (**21-5**). This intermediate undergoes Friedel–Crafts cyclization to

the thioxanthone (**21-6**) in sulfuric acid. The basic side chain is then incorporated by nucleophilic aromatic displacement of chlorine with *N,N*-diethylamino-1,3-diaminoethane. There is thus obtained **lucanthone** (**21-7**) [22]. The metabolic hydroxylation product from this drug is, interestingly, more potent and better absorbed than its parent. That compound, **hycanthone** (**21-8**), can be obtained by fermentation of (**21-7**) with *Aspergillus scelorotium* [23].

Replacement of the nitrogen atom that bears the side chain in the phenothiazine antipsychotic agents described below by trigonal carbon affords compounds that show quite comparable activity; at least one of those agents, **thiothixene** (**24-3**), is widely used in the clinic. Condensation of *para*-chlorothiophenol (**22-1**) with the bromobenzoic acid (**21-4**) gives the thioether (**22-2**). This is then cyclized to the thioxanthone (**22-3**) by means of sulfuric acid. Addition of the Grignard reagent from 1-chloro-3-dimethylaminopropane to the carbonyl group serves to add the required basic side chain (**22-4**). Dehydration of this last intermediate by means of acetic anhydride gives the corresponding olefin as an isomeric mixture. The more potent Z isomer is then separated to afford **chlorprothixine** (**22-5**) [24].
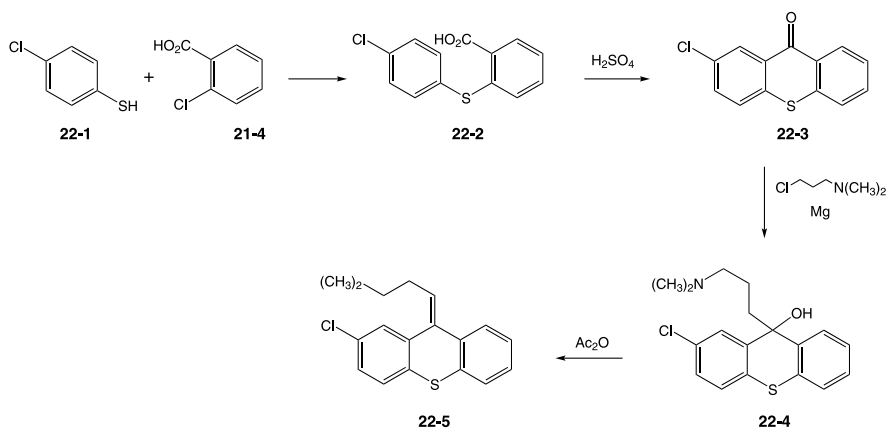
Reaction of the bromobenzoic acid (**23-1**) with chlorosulfonic acid leads to the corresponding sulfonyl chloride; that affords the sulfonamide (**23-2**) on treatment
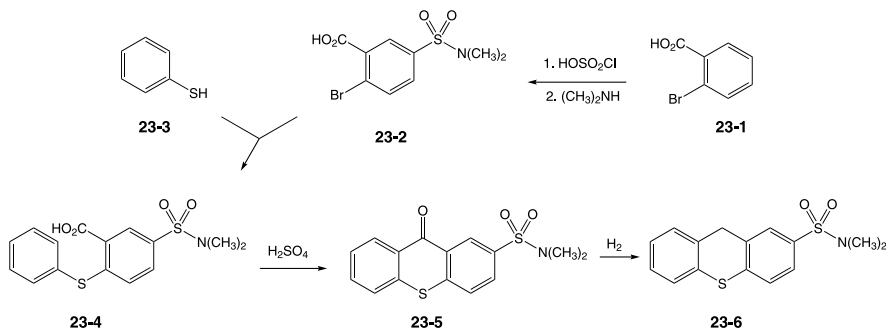
with dimethylamine. That product is then converted to a thioxanthone as above. Thus, coupling with thiophenol (**23-3**) gives the thioether (**23-4**); this gives the tricyclic intermediate (**23-5**) on exposure to sulfuric acid. A somewhat different scheme is used to introduce the side chain in this case. The first step consists of the reduction of the carbonyl group to methylene by catalytic hydrogenation over palladium to give (**23-6**).

Treatment of the reduced intermediate (**23-6**) with butyl lithium leads to the anion from the removal of a proton on the methylene group; reaction of that with methyl acetate affords the methyl ketone (**24-1**), which contains two of the three required side chain carbon atoms. The additional carbon atom and the basic function are incorporated by means of a Mannich condensation. Thus, reaction of (**24-1**) with N-methylpiperazine and formaldehyde leads to the aminoketone (**24-2**). The carbonyl group is then reduced with sodium borohydride and the resulting alcohol is dehydrated by reaction with phosphorus oxychloride in pyridine. In this case, too, the Z isomer is responsible for most of the activity. This is isolated from the resulting mixture of olefins to afford **thiothixene** (**24-3**) [25].
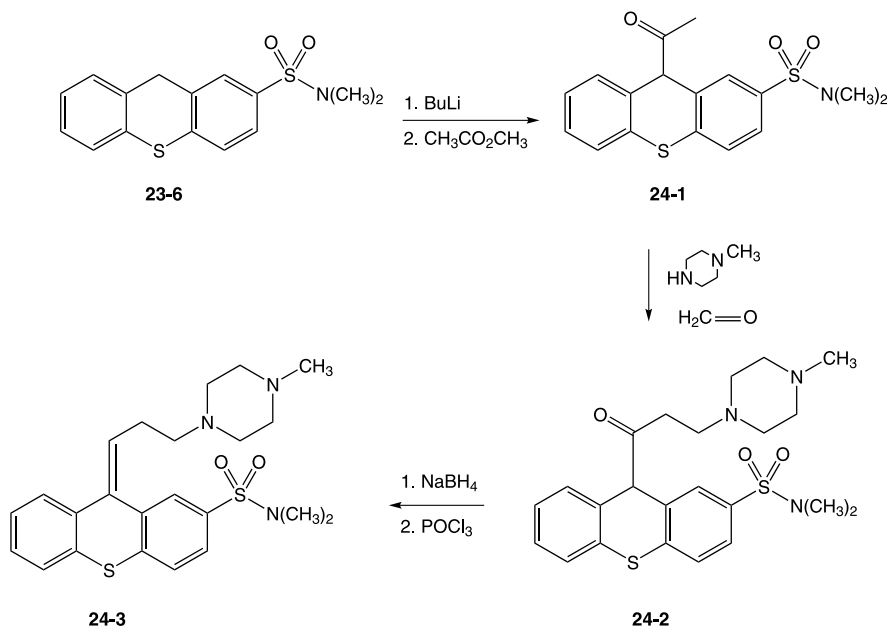
The anion from the parent unsubstituted thioxanthene provides the starting material for a simplified analogue that shows muscle relaxant rather than CNS activity. Alkylation of the anion obtained by treating (**25-1**) with butyl lithium with substituted piperidine (**25-2**) affords **methixene** (**25-3**) in a single step [26].
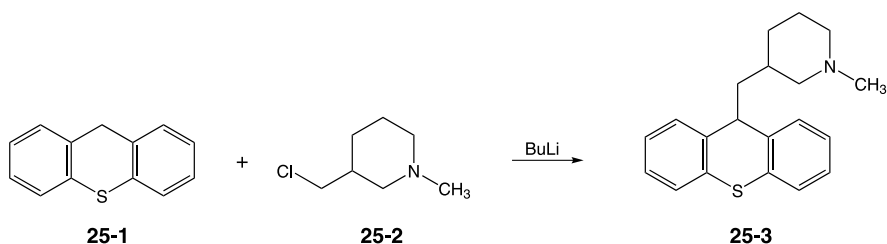
Antipsychotic activity is retained when the heterocyclic ring is enlarged by one carbon. The synthesis of this agent is quite similar to that used for its oxygen analogue, **doxepin** (**5-7**), though with a reversed functionality. The sequence in the present case starts with the alkylation of thiosalicylic acid (**26-2**) with benzyl chloride (**26-1**) to give the thioether (**26-3**). The product is then cyclized by means of polyphosphoric acid to give the ketone (**26-4**). Condensation with the familiar dimethylpropylamne Grignard reagent serves to introduce the side chain (**26-5**). Dehydration of the tertiary alcohol then affords **dothiepin** (**26-6**) as a mixture of isomers [27].
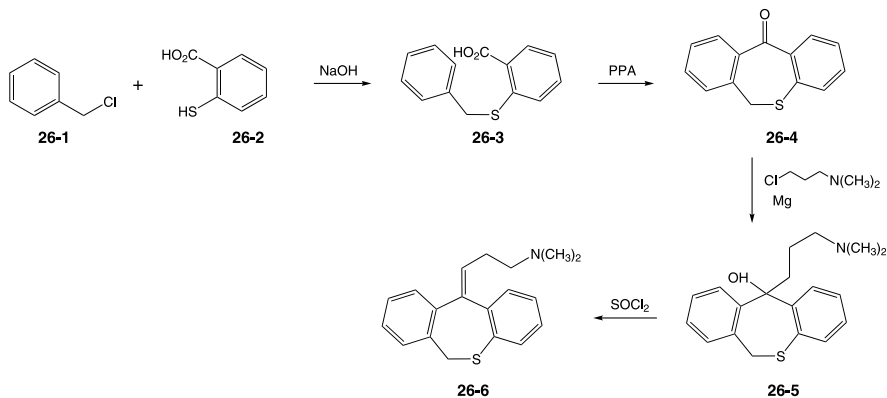
The equivalence of sulfur and oxygen in this ring system carries over to NSAIDs as well. Preparation of the sulfur analogue of **isoxepac** (**6-4**) starts with the alkylation of thiophenol (**27-1**) with benzyl chloride (**26-1**). Cyclization of the intermediate thioether (**27-2**) then affords the homothioxanthone (**27-3**). The carboxyl side chain is then extended by means of the Arndt–Eistert homologation reaction. The acid is thus first converted to its acid chloride by means of thionyl chloride. Reaction with excess diazomethane leads to the diazoketone (**27-4**). Treatment of that intermediate with silver benzoate and triethylamine leads the ketone to rearrange to an acetic acid. There is thus obtained **tiopinac** (**27-5**) [28].
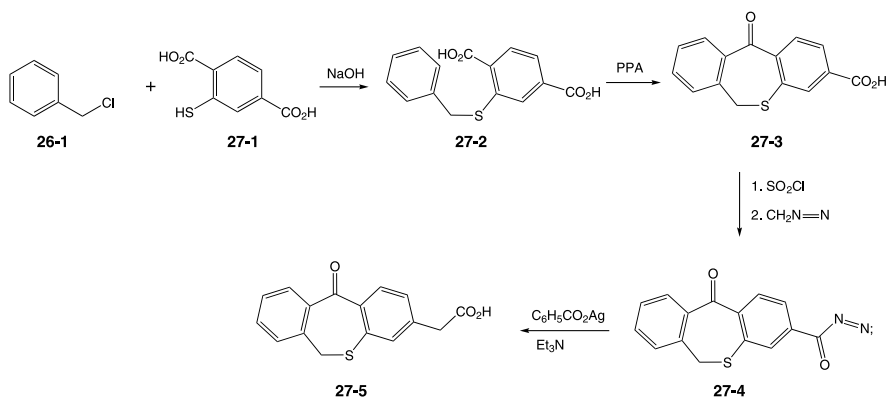
A compound whose structure somewhat stretches the definition in that the hetero-cylic ring is at one end rather than the center of the three-ring array acts as a peroxisome proliferator receptor (PPAR) agonist. This agent, in broad terms, activates the liver enzymes that metabolize fatty acids and as a result lowers serum triglycerides. Reaction of the lithio reagent from 2,3-dimethylthiophene (**28-1**) with benzaldehyde (**28-2**) leads to the carbonyl addition product (**28-3**). The benzylic hydroxyl is next removed by hydrogenation over palladium (**28-4**). This intermediate is then treated with the substituted benzoyl chloride (**28-5**) in the presence of stannic chloride to afford the product from acylation on the carbon with the highest electron density, thus yielding the acylated thiophene (**28-6**). Exposure of the product to boron tribro-mide in the cold leads to the formation of a new ring; the methyl ether on the pendant benzene ring is cleaved to the corresponding phenol in the process (**28-7**). The enolate from the treatment of that phenol with potassium carbonate with the α-bromo-ester (**28-8**) affords the corresponding alkylation product as a mixture of
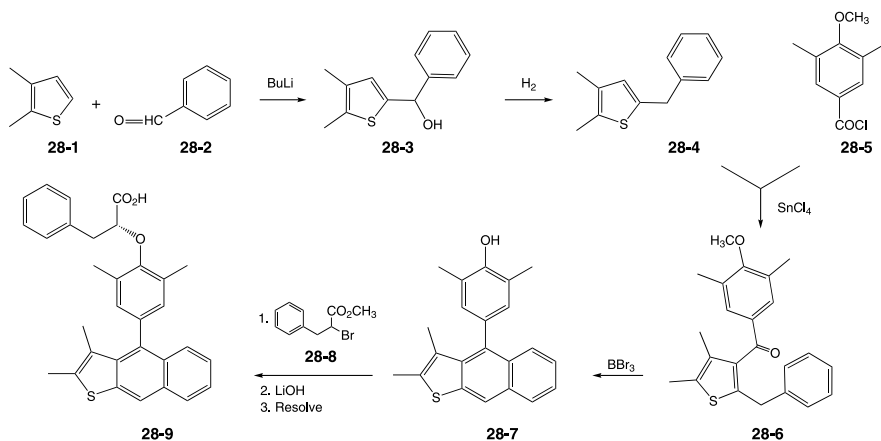
enantiomers. Saponification of the ester affords the corresponding carboxylic acid. Resolution as its salt completes the synthesis of **ertiprotafib** (**28-9**) [29].

13.2. COMPOUNDS CONTAINING TWO HETEROATOMS

13.2.1. Phenothiazines

The various topics discussed in this book have up to this point been arranged as far as possible on the basis of chemical structure; compounds that contain one oxygen and one nitrogen atom have, for example, as a general rule preceded those that contain two nitrogen atoms. The fact that virtually all of the entities that follow show CNS activity combined with the circumstance that phenothiazines comprise a large part of this section require a departure from that approach. The serendipitous discovery of the antipsychotic activity of the phenothiazines in the early 1950s virtually opened the modern era of medicinal chemistry. These will thus be discussed at the outset to preserve historical perspective.

One of the earliest classes of synthetic medicinal agents consists of the antihistamines derived from benzhydrol; the ethylamine moiety present in many of these compounds was included in the belief that it mimicked the same structural fragment in histamine. This may have led to substitution of that side chain on phenothiazine (**29-2**). The product, **diethazine** (**29-3**), in fact shows respectable activity as an antiallergic antihistamine (H_1 histamine antagonist in today's parlance). It is of note, however, that both this and some related ethylamino substituted phenothiazines also exhibit effects on the CNS manifested as sedative and antiemetic activity. The starting phenothiazine can be prepared by the so-called sulfuration reaction that comprises the treatment of diphenylamine (**29-1**) with sulfur and iodine. This transformation may take place via an initial formation of *ortho* iodo aniline derivatives that then undergo displacement by sulfur. Alkylation with 2-chlorotriethylamine of the nitrogen anion from reaction of (**29-2**) with a strong base such as sodium amide affords **diethazine** (**29-3**) [30].
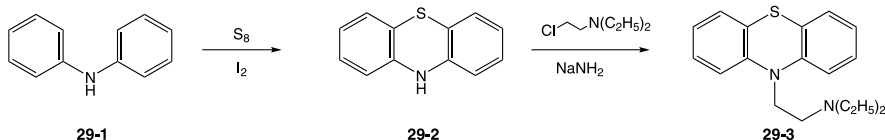
The inclusion of an extra methylene group in the side chain led to compounds with diminished antihistaminic activity. These compounds, however, showed increased CNS activity over that which had been observed with the ethylamino derivatives. This activity was in addition qualitatively different from that manifested by earlier antihistamines. The dearth of animal models for psychoses available at that time means that inspired insight led to the first clinical trials of these compounds as

antipsychotic agents. The efficacy of **chlorpromazine** (**30-5**) and its many analogues led to a revolution in the treatment of mental disease. It is now recognized that this class of drugs acts as dopamine antagonists by binding receptors for that neurotransmitter in the same manner as **haloperidol** and related compounds discussed in Chapter 9 that were, it need be noted, developed after the phenothiazines.

An alternate and more controlled approach to the synthesis of phenothiazines involves sequential aromatic nucleophilic displacement reactions. This alternate scheme avoids the formation of the isomeric products that are sometimes observed to form from the sulfuration reaction when using substituted aryl rings. The first step in this sequence consists of the displacement of the activated chlorine in nitrobenzene (**30-1**) by the salt from *ortho*-bromothiophenol (**30-2**) to give the thioether (**30-3**). The nitro group is then reduced to form aniline (**30-4**). Heating that compound in a solvent such as DMF leads to the internal displacement of bromine by amino nitrogen and the formation of the chlorophenothiazine (**30-4**). Alkylation of the anion from that intermediate with 3-chloro-1-dimethylaminopropane affords **chlorpromazine** (**30-5**) [31].
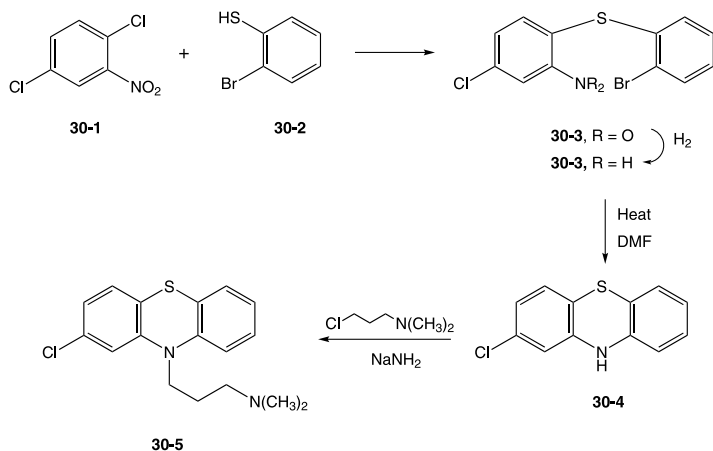
The general scheme is sufficiently flexible to permit the interchange of the order of some of the steps. Thus alkylation of aniline thioether (**30-3**) with 3-chloro-1-diethylaminopropane leads to the intermediate (**31-1**). Ring closure as above by nucleophilic aromatic displacement leads to the antipsychotic drug **chlorproethazine** (**31-2**) [32].
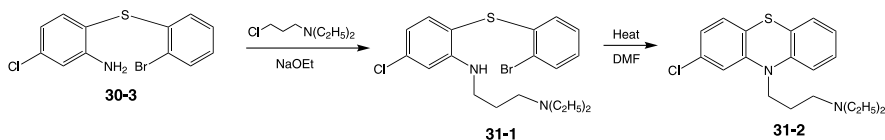
The preparation of a diarylamine required for the synthesis of a phenothiazine via the sulfuration reaction requires the use of an activated chlorobenzene.

The displacement of chlorine from 2-chlorobenzoic acid by nitrogen in substituted aniline (**32-1**) gives the diphenylamine (**32-2**). The carboxyl in the anthranilic acid derivative (**32-2**), having accomplished its activating effect, is next removed by heating to give the intermediate (**32-3**). This gives predominantly the phenothiazine (**32-4**) on treatment with sulfur and iodine; the reaction may well be aided by the presence of the electron donating thioether at the *para* position. Alkylation of nitrogen, again via its anion, with 1-methyl-4-(3-chloropropyl)piperazine (**32-5**) affords **thiethylperazine** (**32-6**) [33].
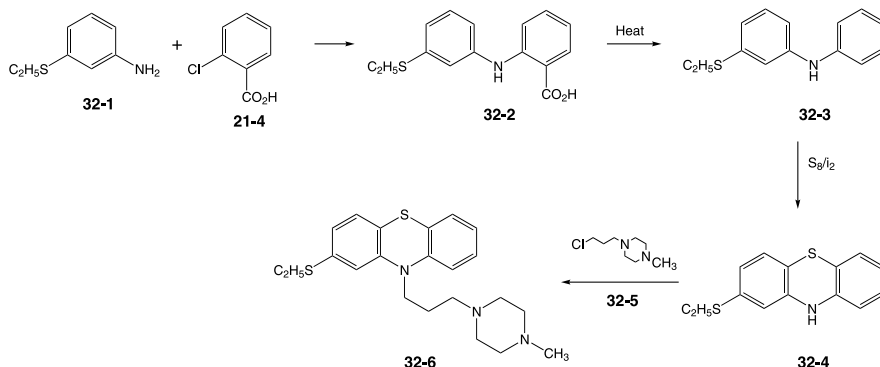
The Smiles rearrangement, which leads to the transposition of sulfur and nitrogen, is used in the synthesis of 3-trifluormethylphenothiazine, (**33-7**). The overall reaction involves the treatment of nitrobenzene (**33-1**) with the aminothiophenol (**33-2**) in the presence of a strong aqueous base to give phenothiazine (**33-6**). The first step in the complex sequence can be visualized as the displacement of the highly activated chlorine in (**33-1**) by sulfur to give the transient thioether (**33-3**) in the presence of a base. The anion from the formamide function in that product then adds to the aromatic ring bearing the nitro group to give the charged spirocyclic intermediate (**33-4**). The negative charge on the carbon bearing the nitro group then returns with the opening of the spiran by the scission of the carbon–sulfur bond to give thiophenoxide (**33-5**). That anion then displaces the nitro group to form the desired phenothiazine (**33-6**);
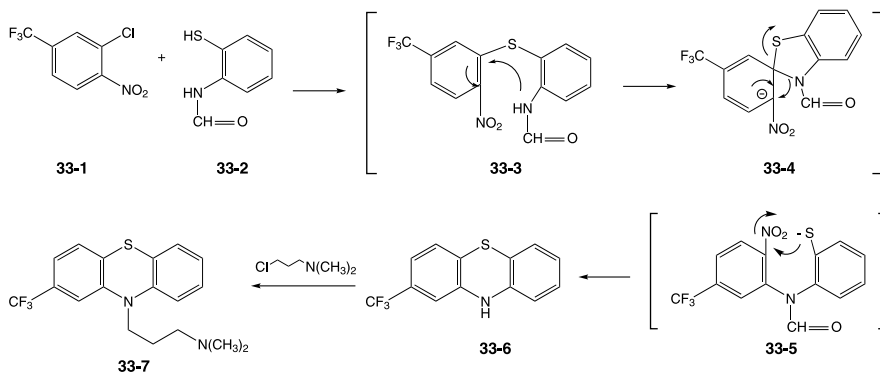
the formamide cleaves under reaction conditions. Alkylation of the anion from (**33-6**) with 3-chloropropyldimethylamine then affords **triflupromazine** (**33-7**) [34].

The reduced basicity of phenothiazine nitrogen requires that even acylation proceed via the anion. The amide (**34-2**) from the methyl thioether (**34-1**) can be prepared, for example, by sequential reaction with sodium amide and acetic anhydride. Oxidation of that intermediate with peracid proceeds preferentially on the more electron-rich alkyl thioether to give the sulfone; this affords the phenothiazine (**34-3**) on hydrolysis of the amide. Complex side chains are most conveniently incorporated in a stepwise fashion. The first step in the present sequence involves reaction of (**34-3**) as its anion with 1-bromo-3-chloropropane to give (**34-4**). The use of that halide with alkylate piperidine-4-carboxamide (**34-5**) affords the antipsychotic agent **metopimazine** (**34-6**) [35].
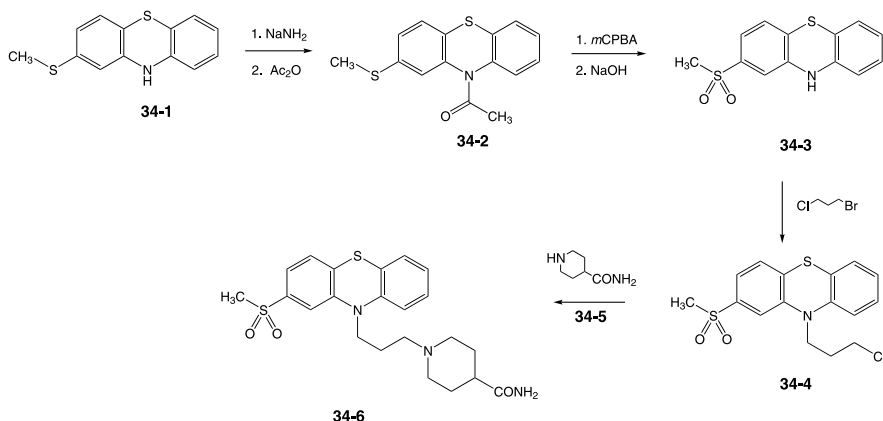
13.2.2. A Dibenzoxazine

A compound whose structure bears some slight resemblance to ertiprotafib (**28-9**) based on a phenoxazine nucleus similarly shows PPAR activity. The fact that the agent also increases sensitivity to insulin has led to its use in treating Type II diabetes. The synthesis of the side chain begins with Emmons–Smith condensation of benzaldehyde (**35-1**) with the ylide from phosphonate (**35-2**) and a base to afford the enol ether (**35-3**) as a mixture of isomers. Hydrogenation of the resulting intermediate reduces the double bond and at the same time removes the benzyl group to afford the free phenol (**35-4**). Reaction of this compound with a hydrolase enzyme leads to selective hydrolysis of the ester that leads to the *S* enantiomer (**35-5**). This kinetic resolution affords the acid as a virtually single stereoisomer. The carboxyl group is then protected for the next step as its isopropyl ester (**35-6**). In a convergent scheme, the anion on nitrogen from unsubstituted dibenzoxazine (**35-7**) and butyl lithium is treated with ethylene oxide (**35-8**). The hydroxyl group on the end of the ethyl group in (**35-8**) is next converted to its methane sulfonate (**35-9**) by means of methanesulfonyl chloride. Displacement of that newly introduced leaving group by the phenoxide from (**35-6**) and potassium carbonate leads to the alkylated derivative (**35-10**). Saponification of the terminal ester then gives **ragaglitazar** (**35-11**) [36].
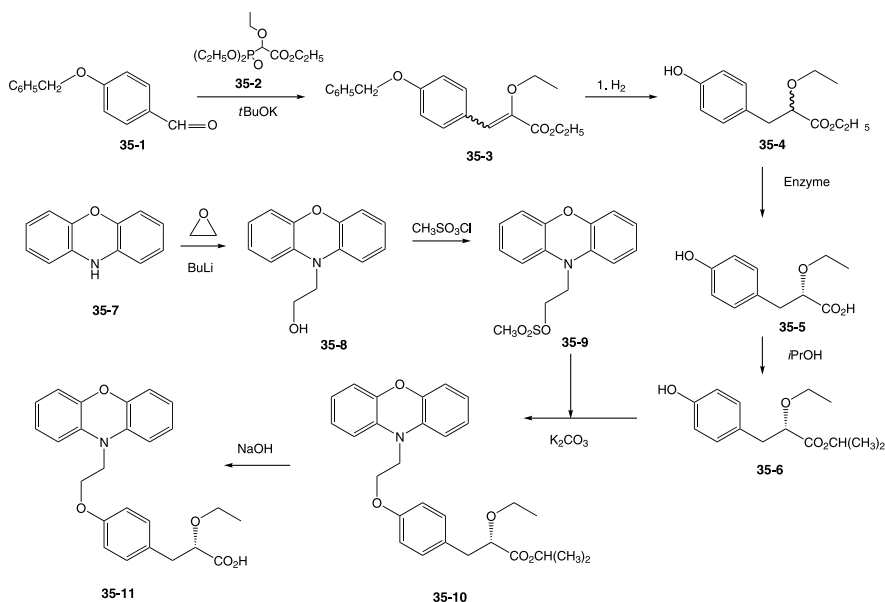
13.2.3. Dibenzodiazepines, Dibenzoxazepines, and a Dibenzothiazepine

Seven-membered rings that contain two heterocyclic atoms have also provided a significant number of CNS agents as foreshadowed in Chapter 12. The Ullman reaction provides the key for preparing the diaryl-amine or -ether starting materials in this series as well. As an example, copper catalyzed coupling of methyl N-methylanthranilate (**36-2**) with nitrobromobenzene (**36-1**) leads to the arylaniline (**36-3**). The ester is then saponified (**36-4**) and the nitro group reduced to the corresponding amine (**36-5**). That product cyclizes to the lactam (**36-6**) on heating. A strong base preferentially removes
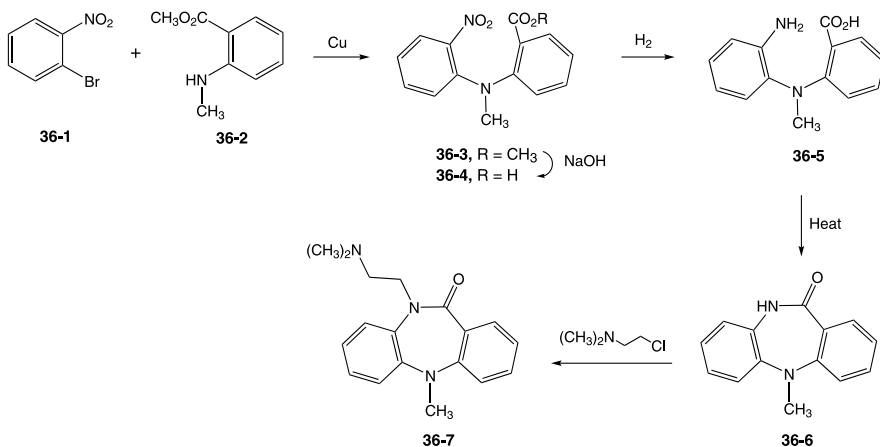
the proton on the lactam nitrogen to form an anion. Alkylation with 2-chloroethyl-dimethylamine then affords **dibenzepin** (**36-7**), a compound that shows antidepressant activity [37].

The fact that antipsychotic agents control rather than cure schizophrenia means that most patients may well be treated with dopamine antagonist drugs for the rest of their lives. Such long-term use is unfortunately often accompanied by the emergence of severe side effects that can be traced to the same antagonism of dopamine that makes the drugs effective in the first place. The undesired effects are, it is believed, a reflection of the lack of selectivity of the antidopamine action. The series of dibenzo heterocycles substituted with a pendant piperazine ring discussed below comprise a set of significantly better-tolerated antipsychotic agents. This may be due to enhanced selectivity for a subset of dopamine receptors as well as the antagonist action at the serotonin receptors.

The first step in one synthesis of the antipsychotic drug **clozapine** (**37-5**) involves Ullman coupling of anthranilic acid (**37-1**) with 2,4-dichloronitrobenzene (**30-1**) to give the substituted anthranilate (**37-2**). The carboxyl group is then converted to the *N*-methylpiperazinamide (**37-3**) via a suitably activated intermediate as, for example, the imidazolide obtained by reaction with carbonyldiimidazole (CDI). The nitro group is then reduced to amine (**37-4**) by means of catalytic hydrogenation. Intramolecular Schiff base formation catalyzed by toluenesulfonic acid then completes the synthesis of **clozapine** (**37-5**) [38].
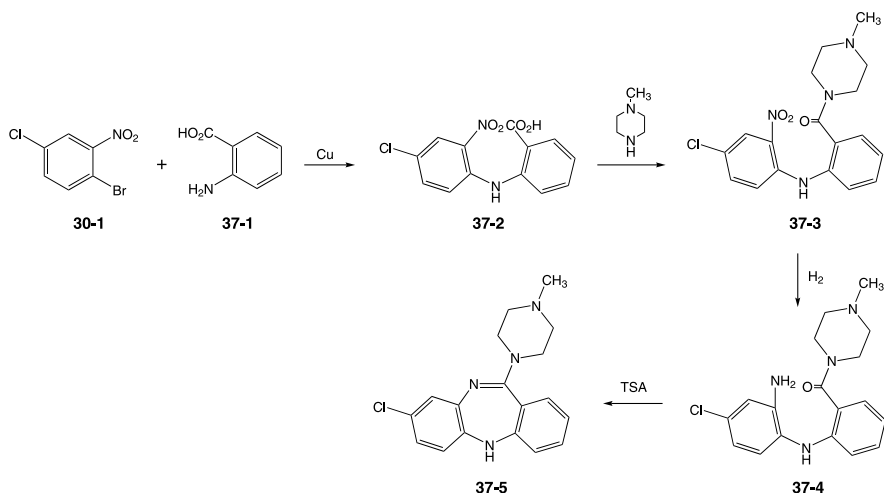
A considerable degree of freedom prevails as to the nature of the one-atom bridge since activity is retained when this is oxygen, sulfur, or even carbon. The displacement of chlorine in *ortho*-chloronitrobenzene (**38-1**) by *para*-chlorophenoxide (**38-2**) leads to the starting material (**38-3**). Reduction of the nitro group leads to the aniline (**38-4**). Reaction of that intermediate with phosgene in the presence of triethylamine gives the corresponding isocyanate (**38-5**). The addition of *N*-methylpiperazine to the isocyanate function leads to a urea and thus the product (**38-6**).

Treatment of the product with phosphorus oxychloride leads to a cyclodehydration reaction possibly via the imino chloride. There is thus obtained the antipsychotic compound **loxapine (38-7)** [39].
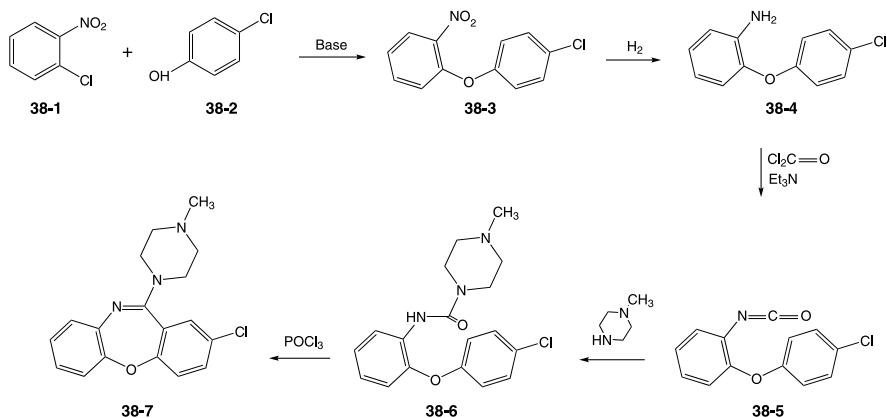
The preparation of the *N*-desmethyl analogue, **amoxapine (39-7)**, illustrates an alternate approach in which the oxygen ether linkage is formed last. Reaction of the imidazolide (**39-2**) from 2,4-dichlorobenzoic acid (**39-1**) and carbonyldiimidazole with *ortho*-aminophenol (**39-3**) gives the benzamide (**39-4**). This is then converted to its imino chloride (**39-5**) with the ubiquitous phosphorus oxychloride.[1] Treatment of the product with piperazine leads to the amidine (**39-6**), probably by an addition-elimination sequence. Copper catalyzed displacement of chlorine by phenoxide closes the ring; there is thus obtained **amoxapine (39-7)** [40].

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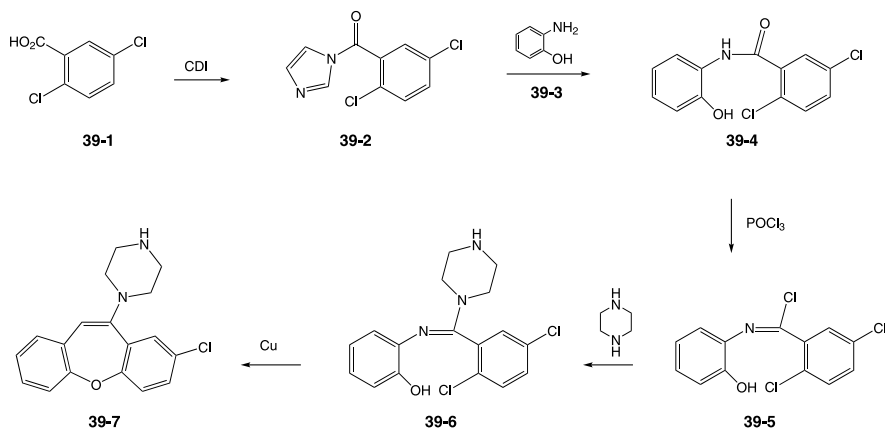
[1]The author can personally attest to the deleterious effect of this reagent on human skin.

Yet another approach to these compounds consists of substituting the piperazine ring onto the preformed heterocyclic moiety. Ullman condensation of the substituted thiosalyciclic acid (**40-1**) with *ortho*-chloronitrobenzene results in the displacement of chlorine by thiophenoxide and the formation of the thioether (**40-2**). The nitro group in this last intermediate is then reduced to an aniline (**40-3**); the resulting amino acid is then cyclized thermally to the lactam (**40-4**). Treatment of that with phosphorus oxychloride gives the imino chloride (**40-5**). Reaction with *N*-methylpiperazine leads to the replacement of chlorine by nitrogen and the formation of **clothiapine** (**40-6**) [39].
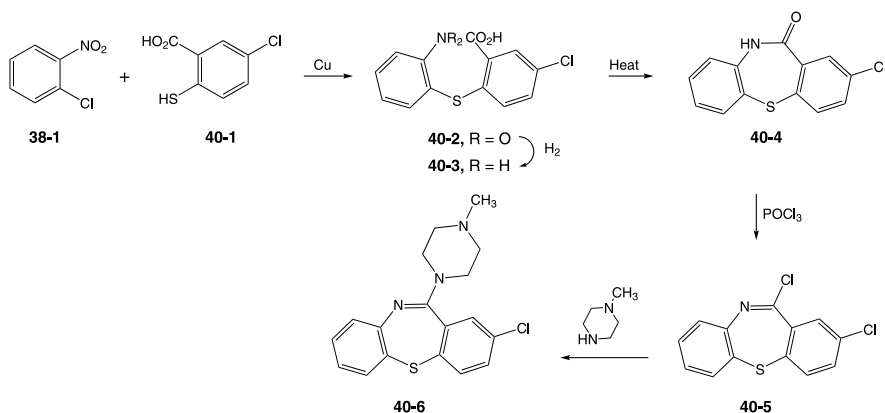
The reduced side effects of antipsychotic agents such as **quetiapine** (**41-4**) have been attributed to the agents' selective action on α-2 adrenergic and serotonin H_2 receptors. The structure of this compound differs from the preceding examples largely by the oxygenated side chain on the terminal piperazine nitrogen. Treatment of the unsubstituted dibenzthiapine (**41-1**) with phosphorus oxychloride
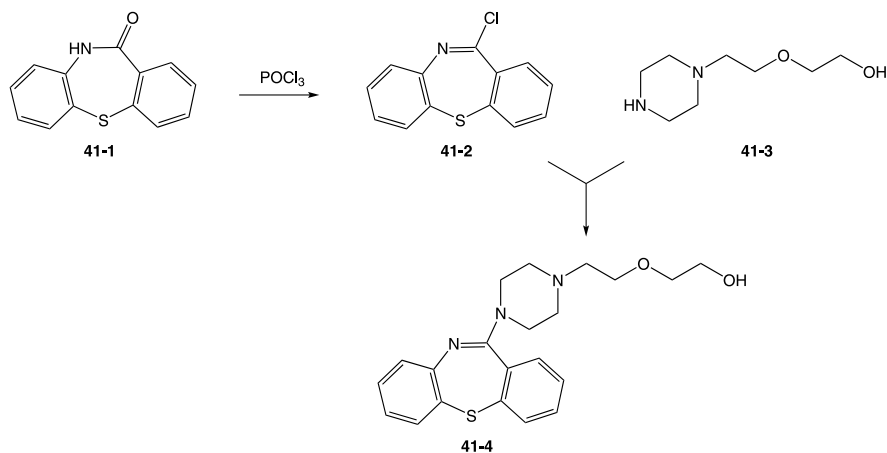
leads to the enol chloride (**41-2**). The displacement of halogen by the secondary nitrogen in piperazine (**41-3**) leads to **quetiapine** (**41-4**) [41].

13.3. PYRIDINE-BASED FUSED TRICYCLIC COMPOUNDS

Benzene rings often serve in drugs simply as flat, relatively electron-rich moieties. Many examples have been noted thus far where such rings can be replaced by heterocycles that have some degree of aromatic character.

An analogue related to the anthraquinone topoismerase-2 inhibitor antitumor drug **mitoxantrone** (Chapter 3), in which one of the benzene rings is replaced by pyridine, perhaps not surprisingly, retains antitumor activity. Reaction of the lithio reagent from 4-chlorofluorobenzene (**42-2**) with the pyridine equivalent (**42-1**) of phthalic anhydride affords the acylation product (**42-3**). Treatment with an acid leads to internal acylation and the formation of the aza-anthraquinone (**42-4**). Condensation of this intermediate with the substituted hydrazine (**42-5**) leads to the formation of the fused pyrrazole (**42-6**). The regiochemistry of this reaction would suggest that the first step involves the displacement of halogen and is thus guided by a greater ease of replacing fluorine over chlorine; ordinary imine formation then closes the ring. Displacement of the remaining halogen by *N,N*-dimethyl ethylenediamine (**42-7**) completes the synthesis of **topixantrone** (**42-8**) [42].
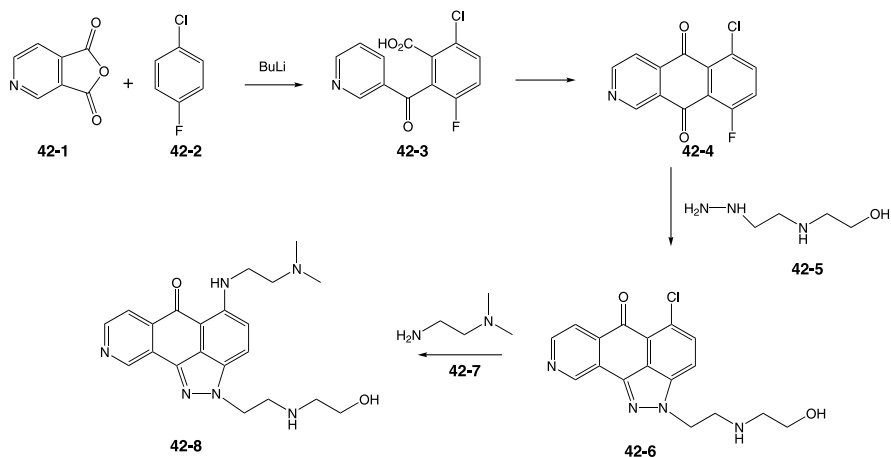
In a related vein, one of the benzene rings in **dibenzepin** (**36-7**) can be replaced by pyridine. In a one-pot reaction, condensation of the 2-chloronicotinic acid (**43-2**) with *ortho*-phenylenediamine (**43-1**) leads to the lactam (**43-3**). The order in which the two steps, aromatic displacement and amide formation, take place has not been elucidated. Simple alkylation of the anion from the product with 3-chloro-2-(*N,N*-dimethylamino)propane (**43-4**) affords the antidepressant agent **propizepine** (**43-5**) [43].
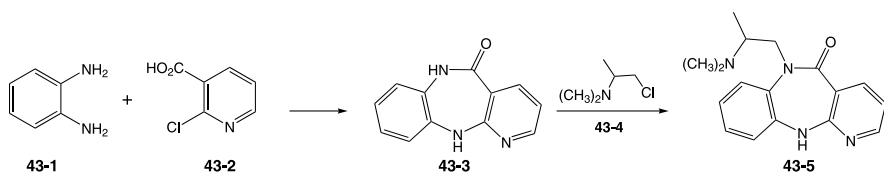
The antidepressant agent **tampramine** (**44-6**) can be viewed as a distant analogue of **imipramine** that contains an extra benzene ring and two additional nitrogen atoms. The preparation of this compound starts by Ullman coupling of chloropyridine (**44-1**) with the aminobenzophenone (**44-2**) more frequently used for benzodiazepine syntheses. Reduction of the nitro group in the product (**44-3**) leads to a diamine (**44-4**) that readily cyclizes to form the pyridodiazepine (**44-5**). Alkylation of the anion from the treatment of this with sodium hydride with 3-chloro-1-dimethylaminopropane affords **tampramine** (**44-6**) [44].
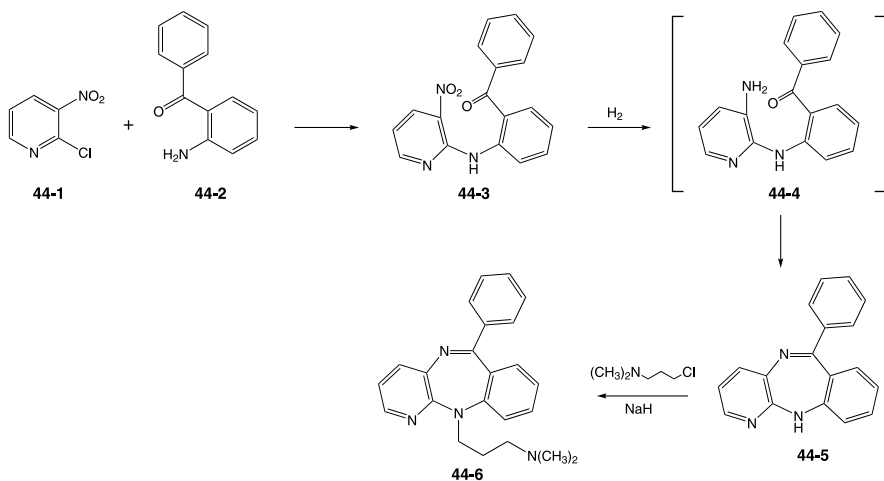
The success of the antiallergy mediator release inhibitor cromolin sodium (Chapter 7) led to investigations on other analogues that incorporated a chromone moiety. Warming the chromone (**45-1**) in aqueous morpholine leads to a Dimrroth-like rearrangement; the first step comprises opening the heterocyclic ring to afford the transient cyanoaldehyde (**45-2**). The nucleophilic phenol then adds back to the nitrile. The initial imine then reorganizes to afford the amino-aldehyde (**45-3**). Condensation of that intermediate with ethyl cyanoacetate leads initially to the Knoevnagel product (**45-4**). This proceeds to the fused pyridine (**45-5**) under reaction conditions by the addition of the amine to the adjacent nitrile. Saponification of the ester then proceeds to afford **amlexanox** (**45-6**) [45].

45-1   **45-2**   **45-3**

45-4

45-5, R = Et
45-6, R = H
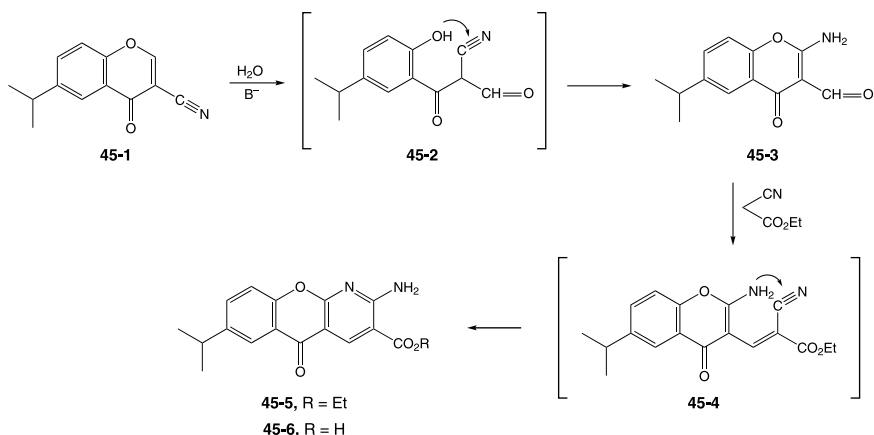
The structures of the non-nucleoside reverse transcriptase inhibitors (NNRTI) that comprise an ingredient in the three-part drug cocktails for treating HIV have little in common, as noted in Chapter 9. The bispyridodiazepinone **nevirapine** (**46-5**) was the first NNRTI approved for treating HIV and still finds extensive use. The first step in the syntheses comprises the acylation of the aminopyridine (**46-1**) with the chlorinate nicotoyl chloride (**46-2**) to afford amide (**46-3**). Treatment of the product with cyclopropylamine leads to the selective displacement of the halogen adjacent to the activating carbonyl (**46-4**). The anion from the reaction of that intermediate then displaces

46-1   **46-2**   **46-3**
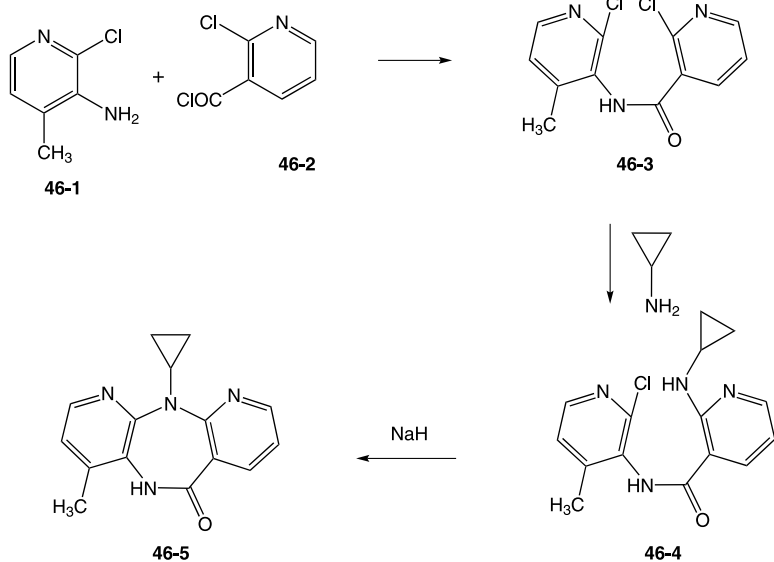
46-5   **46-4**

the corresponding halogen on the adjacent pyridyl function to form the diazepinone ring. This then affords the NNRTI **nevirapine** (**46-5**) [46].

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CHAPTER 14

BETA LACTAM ANTIBIOTICS

The first indication that molds produce substances that inhibit bacterial growth predates the discovery of the antibacterial drug prontosil by a good half-decade. The compound responsible for that activity, **penicillin** (**1-1**), was, however, not actually isolated until the late 1930s and developed for clinical use until the early 1940s. The poor stability and short biological half-life of this drug led initially to the development of a series of salts intended to remedy those problems. The development many years later of methods for producing the bare penicillin nucleus led to the synthesis of a host of analogues by manipulation of the amide side chain intended to approach that problem as well as the fact the antibacterial spectrum of natural penicillins was restricted to Gram positive organisms. An intense worldwide search for other antibiotic producing molds, mostly in soil samples, led to the discovery of the beta lactam cephalosporin C, which is active against Gram negative bacteria; the development of methods for obtaining the bare cephem nucleus led to clinically effective analogues. The very large number of penicillin and cephalosporin analogues that differ only in the amide substituent will be touched on only briefly since most of the chemistry lies in the methods for preparing the side chains.

1-1
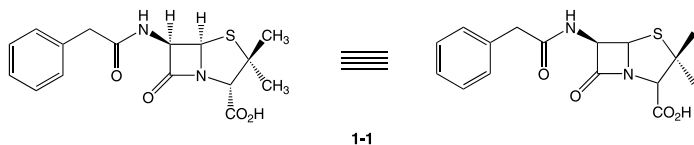
The extremely low toxicity of these drugs to mammalian species follows directly from the mechanism by which beta lactams as a class inhibit bacterial growth. This devolves on the fact that bacteria, like plants, depend on a cell wall for their structural integrity; a cell membrane that is fundamentally different fulfills this function in higher species. A crucial part of such cell walls consists of highly cross-linked peptidoglycans in which peptide chains, which include D-alanine fragments, provide most of the cross-links. In brief, the beta lactams act as false substrates in the construction of the cross-linking of the peptides. The very reactive beta lactam function leads to an irreversible blockade that, in effect, inhibits the formation of the cell walls required for bacterial replication. The fact that the stereochemistry of the penicillins mimics that of D-amino acids further reduces the toxicity since the biochemistry of eukariotic species is based virtually exclusively on L-amino acids. A small number of individuals, it should be added, do manifest allergic reactions, which may verge on the catastrophic, to this class of drugs.

14.1. PENICILLINS

Penicillin is but one of a series of closely related compounds isolated from fermentation broths of *Penicillium notatum*. This compound, also known as **penicillin G (1-1)** or benzyl penicillin, is quite unstable and quickly eliminated from the body. Initial approaches to solving these problems, as noted above, consisted of preparing salts of the compound with amines that would form tight ion pairs that in effect provided a controlled release of the active drug. Research on fermentation conditions aimed at optimizing fermentation yields succeeded to the point where penicillin G or **penicillin V (26-1)**, in which the phenylacetyl group is replaced by phenoxyacetyl, is now considered a commodity chemical. Another result of this research was the identification of fermentation conditions that favored the formation of the deacylated primary amine, 6-aminopenicillanic acid (**2-4**) or 6-APA, a compound that provided the key to semisynthetic compounds with superior pharmaceutical properties than the natural material. An elegant procedure for the removal of the amide side chain proved competitive with 6-APA from fermentation. This method, which is equally applicable to penicillin V, starts by conversion of the acid to the corresponding silyl ester (**2-1**). Treatment of that compound with phosphorus pentachloride in the
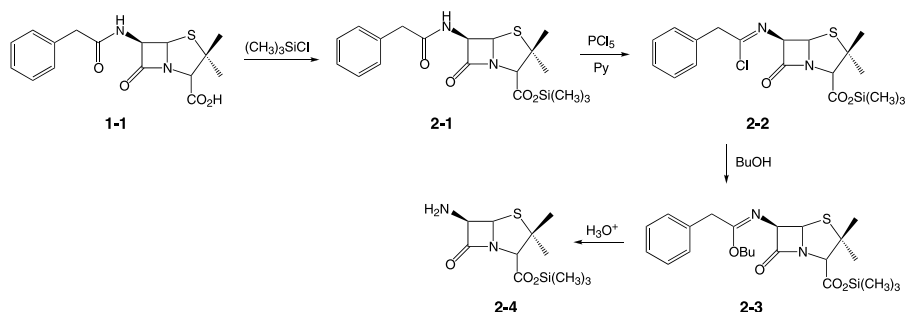
presence of a base leads to the imino chloride (**2-2**); selectivity over the cyclic lactam can be ascribed to the fact that the latter cannot enolize. Solvolysis of the product in butanol leads to the iminoether (**2-3**); the silyl ether is converted to the acid under reaction conditions. Hydrolysis of this last intermediate with an aqueous acid cleaves the iminoether function to afford the free primary amine and thus 6-APA (**2-4**) [1].

The same functionality that is responsible for the activity of this class of antibiotics, the fused azetidone ring, makes for chemical reactivity and thus instability. Many bacteria in addition possess specialized enzymes, the beta lactamases, that deactivate the drugs by cleaving that reactive bond. Several semisynthetic analogues thus include quite bulky groups so as to provide steric hindrance about the beta lactam function to decrease its lability. The chemical reactivity of the lactam function also means that special precautions must be employed in the acylation reactions used to prepare analogues, though the reactions themselves involve standard activated derivatives of the side chains such as acid chlorides or mixed anhydrides. (In the interest of uniformity, analogues are shown as carboxylic acids; many beta lactams, it should however be noted, are provided commercially as their potassium salts.) Acylation of 6-APA, (**2-4**), with the acid chloride from 2,6-dimethoxybenzoic acid, for example, leads to **methicillin** (**3-1**) [2] Reaction with an activated derivative from 2-methyl-5-(2-chlorophenyl)isoxazole carboxylic acid gives **cloxacillin** (**3-2**) [3]. These drugs show decreased sensitivity to beta lactamase. It is of passing interest that the former drug provides the standard for penicillin resistance as noted by the acronym MRSA (Methcillin Resistant *Staph. Aureus*).

Acylation of 6-APA with an amino acid leads to a compound that bears some resemblance to a dipeptide. The coupling product with *D*-phenylglycine shows an enhanced antibacterial spectrum, possibly as a result of a better fit to the cell wall cross-linking enzyme. The compound also shows improved oral absorption. One synthesis starts with the acylation of 6-APA with the acid chloride (**3-3**) from *D*-2-azidophenylacetic acid. Catalytic reduction of the product (**3-4**) affords **ampicillin** (**3-5**) [4]. An analogous scheme leads to **amoxycillin** (**3-6**), a widely used drug that is reasonably well absorbed on oral administration.
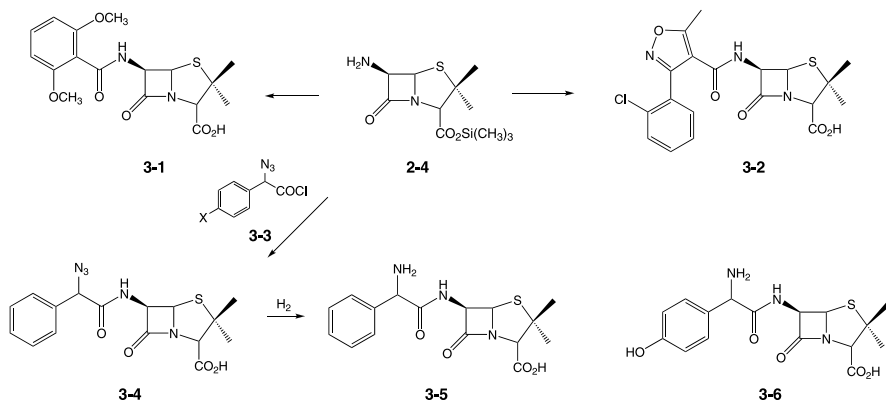
Highly polar water soluble organic compounds are often poorly absorbed from the GI tract. Reducing the polarity of such compounds results in increased solubility in lipid membranes and may thus increase oral absorption. The ubiquity of esterases in serum makes esters particularly well suited for converting acids to less polar derivatives; the enzymes should convert the circulating drug that has been absorbed to the free acid required for biological activity. Esters from acid chlorides such as (**4-1**) from formaldehyde hydrate have been found to be particularly suitable for beta lactams. Hydrolysis of the pivaloyl group leads to a derivative that spontaneously reverts to the free acid; hydrolysis of the other ester bond of course leads to the penicillin acid directly. The first step in one route to such compounds starts with the alkylation of the salt from benzyl penicillin (**1-1**) with chloromethyl pivalate (**4-1**) to give the derivative (**4-2**). This intermediate is then subjected to the side chain removal sequence outlined above (**2-2** → **2-4**) to afford the 6-APA derivative (**4-3**). Acylation of this compound with the acid chloride from *D*-phenylglycine gives the orally active antibiotic **pivampicillin** (**4-4**) [5].
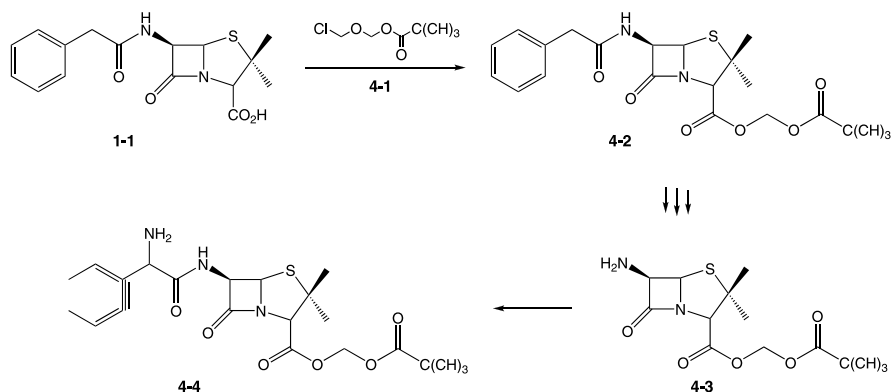
Penicillin and its first generation of semisynthetic analogues are active mainly against Gram positive bacteria. The antibacterial spectrum is somewhat broadened,
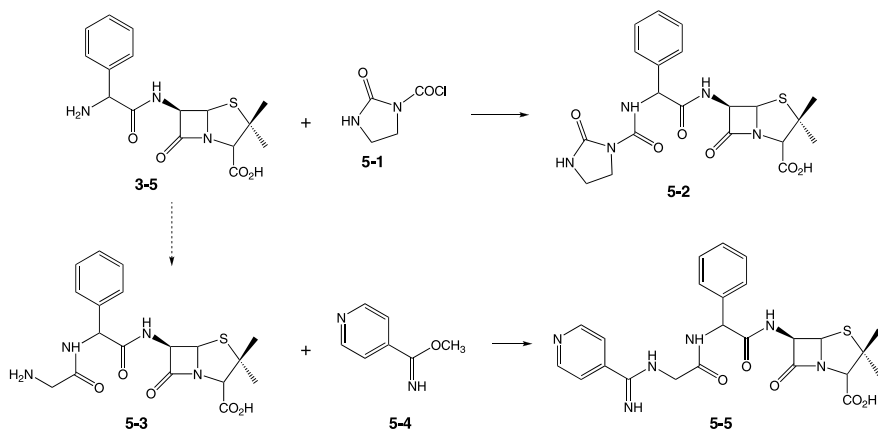
as noted above, by including functionality in the amide side chain. Coupling additional polar moieties onto the phenylglycine amine leads to a further broadening of the antibacterial spectrum. Thus, acylation of ampicillin (**3-5**) with the carbonyl chloride derivative (**5-1**) from imidazolone affords **azlocillin** (**5-2**) [6]. In a similar fashion, condensation of the glycine derivative (**5-3**) from ampicillin with the iminoether (**5-4**) from 4-cyanopyridine leads to **pirbenicillin** (**5-5**) [7]. Both of these compounds are active against *pseudomonas* as well as against the usual Gram positive organisms.

A free carboxylic acid group also enhances the antibacterial spectrum in the penicillin series. Acylation of 6-APA (**2-4**) with the half-acid chloride (**6-1**) from benzyl phenylmalonate leads to the amide (**6-2**). Removal of the benzyl protecting group by catalytic hydrogenation [8] or by enzymatic hydrolysis [9] affords **carbencillin** (**6-3**). A similar sequence starting with 3-thiophenylmalonic acid leads to the considerably more potent analogue **ticarcillin** (**6-4**) [10].
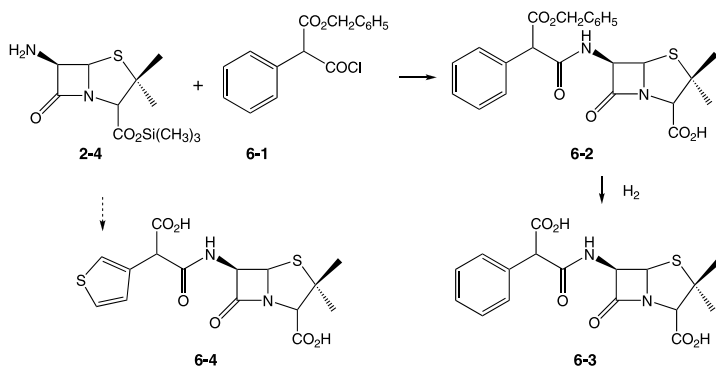
Antibacterial activity is retained when the relatively complex amide side chains are replaced by a simple heterocycle amidine. The required reagent (**7-2**) is prepared by reaction of azepine formamide (**7-1**) with oxalyl chloride. Condensation of the product with 6-APA (**2-4**) leads to the formation of the amidine and thus **amdinocillin** (**7-3**) [11].
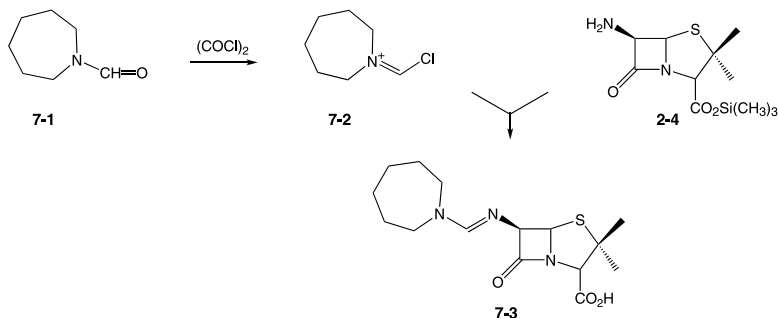
The finding that the addition of a methoxyl group at the 6-α-position significantly enhances resistance to bacterial beta lactamase actually traces to the cephalosporin

series with the discovery of a series of fermentation products, the cephamycins, that bear this substituent. The preparation of the semisynthetic cephalosporin derivative **cefoxitin (35-6)** that carries this substituent will be found later in this chapter.

The preparation of an analogous penicillin derivative starts with the protection of 6-APA, **(2-4)** as its benzyl ester. Reaction of the product with formic acid in the presence of DCC gives the amide **(8-1)**. Treatment of that intermediate with phosgene in the presence of *N*-methylmorpholine converts the amide to the corresponding isocyanate **(8-2)** with retention of the stereochemistry. The combination of the adjacent carbonyl and the isocyanate group facilitates the formation of anions at the 6 position. Thus reaction of **(8-2)** with methylmethoxycarbonyl disulfide in the presence of powdered potassium carbonate leads to the 6-thiomethyl ether **(8-3)**; the α stereochemistry of sulfur is a consequence of the approach from the more open side of the molecule rather than the retention of stereochemistry by the carbanion. Reaction of the isocyanate grouping with toluenesulfonic acid monohydrate achieves selective conversion of the isocyanate back to a primary amino group to give **(8-4)** without affecting the presumably more reactive azetidone. Treatment of that product with mercuric chloride in methanol in the presence of a base leads to the fragmentation of the carbon–sulfur bond and the formation of a transient carbocation. This last adds methanol, again from the open side, to give the key 6α-methoxy intermediate **(8-5)**. The primary amino group at the 6 position is then acylated with the half-acid chloride **(8-6)** from benzyl thiophenemalonic acid to give the amide **(8-7)**. Reductive debenzylation of this last intermediate affords the antibiotic **temocillin (8-8)** [12].
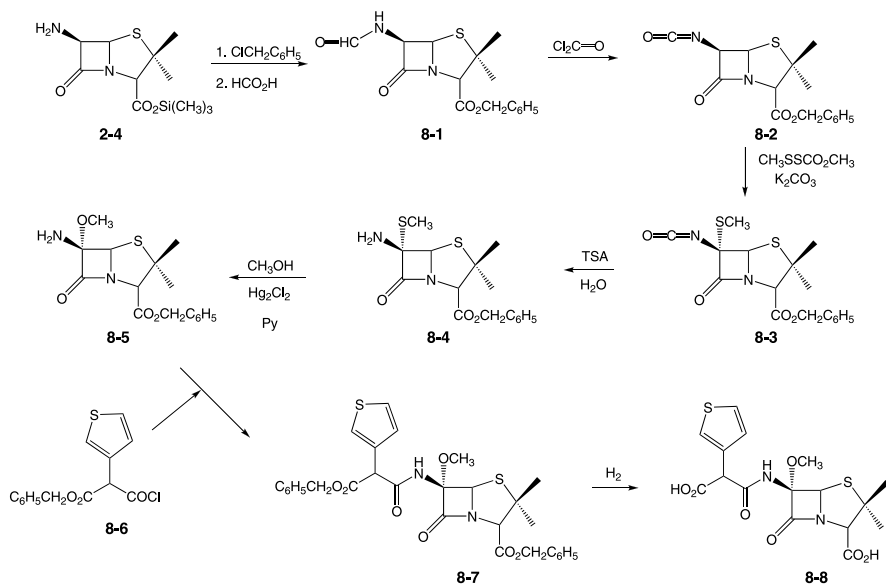
Some penicillin derivatives lacking nitrogen at the 6 position in which the ring sulfur atom is oxidized to a sulfone act as inhibitors of bacterial beta lactamase.

These agents would be used as adjuncts to beta lactams since they have no antibacterial activity in their own right. A key reaction in the synthesis of each compound involves the replacement of the amine at 6 and the protection of that position as a mono- or di-halide. Thus reaction of 6-APA (**2-4**) with nitrous acid gives the diazonium salt (**9-1**); this is converted to the dibromide (**9-2**) on treatment with bromine. The ring sulfur is then oxidized with permanganate to the sulfone (**9-3**). Hydrogenolysis of the product replaces the two bromine atoms by hydrogen to afford **sulbactam** (**9-4**) [13].
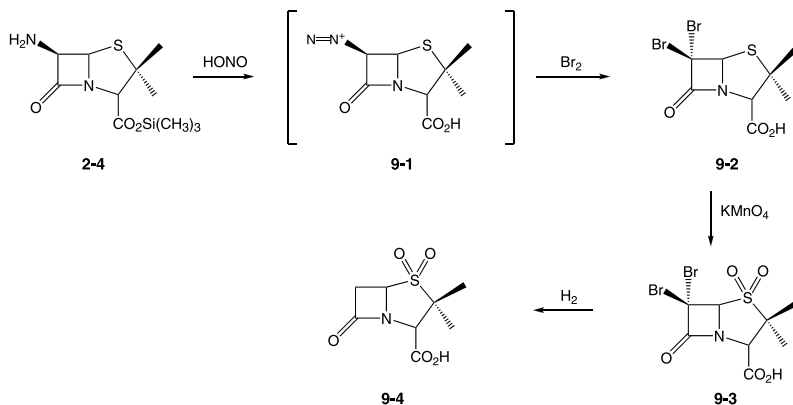
A subsequent analogue involves the substitution of a heterocyclic moiety onto one of the geminal methyl groups. The scheme starts with the diazotization of 6-APA in the presence of excess bromide ion to give the monobromo derivative (**10-1**). Controlled oxidation of sulfur as, for example, with periodate leads to the sulfone (**10-2**). The carboxyl group is then protected as its *para*-nitrobenzyl ester (**10-3**), a group often used in beta lactam chemistry. The bromide at position 7 is then removed by catalytic hydrogenation over palladium to give (**10-4**). The thiazoline oxide ring opening reaction that follows was first developed in work aimed at the conversion of penicillins to cephalosporins; a closely related ring opening is noted below in the discussion of that rearrangement. Thus, reaction of sulfoxide (**10-4**) with 2-mercaptobenzothiazole leads to the dislufide (**10-5**). (The reaction may involve first the formation of a ring opened vinyl sulfinic acid by an initial abstraction of a proton on one of the geminal methyl groups.) Treatment of the dislufide with cuprous chloride proceeds via heterolytic cleavage of the disulfide bond. The thus-generated sulfur radical then adds back to the vinyl group to reform the thiazoline ring. Capture of chloride present in the reaction medium completes the formation of the observed product (**10-6**). The reasons for the preferential formation of the β-chloromethyl isomer are not immediately apparent. Construction of the side chain heterocycle starts with the displacement of chlorine in (**10-6**) with sodium azide to afford the cumulene (**10-7**). The ring oxygen is then oxidized to a sulfoxide by reaction with permanganate (**10-8**). The azide function in that intermediate undergoes 1,3-dipolar cycloaddition when treated with acetylene to form a 1,2,3-triazole

ring (**10-9**). Saponification with a dilute base then cleaves the nitrobenzyl protection group to afford the beta lactamase inhibitor **tazobactam** (**10-10**) [14].
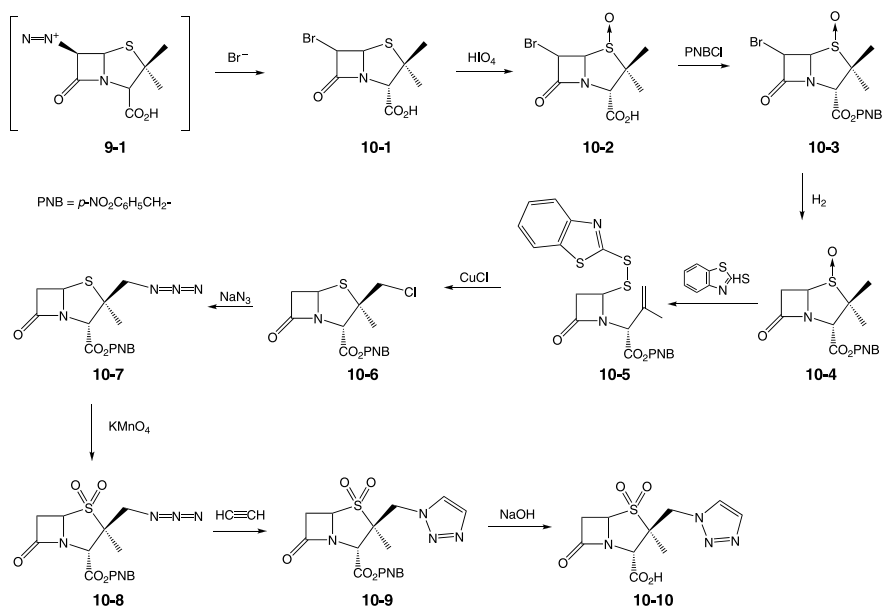
The search for new antibacterial agents in fermentation broths continued long after the identification of the cephalosporins. One result of this continuing research was the identification of a very potent, broad-spectrum beta lactam antibiotic that is unusually resistant to beta lactamase. The structure of this compound, **thienamycin** (**12-8**), at first glance resembles that of a penicillin. It differs, however, in many respects, most markedly by the fact that the dimethylthiazolidine ring is replaced by pyrroline and the amine at the βC-6 position is replaced by an α-hydroxyethyl group. Stability problems with the pure drug, traceable to the lability of the thioenolether function, precluded the use of the compound as a drug. One synthesis of the far more stable amidine analogue **imipenem** (**12-7**) illustrates the chemistry used for the total synthesis of beta lactam antibiotics.

Reaction of the ethyl ester (**11-1**) of acetonedicarboxylate with benzylamine in the presence of a molecular sieve gives the corresponding enamine (**11-2**). Condensation of that product with diketene (**11-3**) gives the acylation product (**11-4**) in which the olefin has shifted to form an imine. Treatment of that product with sodium borohydride leads to the stereospecific reduction of both the imine and keto functions, probably by way of the conjugated enol form, to give the aminoalcohol (**11-5**). Reaction of that with an acid leads to the formation of the six-membered lactone. Reaction with the alternate carbethoxy group would lead to an unstable propiolactone. The benzyl protecting group on the amine is then removed by catalytic hydrogenation to afford the intermediate (**11-6**). Reaction of this last intermediate with benzyl alcohol in the presence of an acid proceeds at the more reactive lactone carbonyl group to

give the corresponding benzyl ester. There is thus obtained the amino acid (**11-7**). The beta lactam ring is then closed by internal amide formation catalyzed by cyclohexylcarbodiimide, a reagent originally developed for just such reactions, to afford (**11-8**). The lactam function is then protected by conversion to its *tert*-butyldimethylsilyl (*t*BDMS) derivative and the benzyl protecting group removed reductively to give the beta lactam (**11-9**). The sequence for adding the two additional carbon atoms for the fused ring starts by activation of the carboxyl group in (**11-9**) by conversion to an acylimidazole by reaction with carbonyldimidazole (CDI). Treatment of the activated malonate, Meldrum's acid (**11-10**), with that intermediate leads to the corresponding acylation product. Acidic workup of the product leads to the generation of the malonic acid by hydrolysis of the acetonide; the resulting acylmalonic acid decarboxylates to give the two-carbon addition product. The free carboxylic acid is then esterified to the *para*-nitrobenzyl derivative; hydrolysis of the silyl protecting group then affords (**11-11**). The stereochemistry of the hydroxyethyl group, which traces back to the cyanobrohydride reduction, is in fact the reverse of that required for good antibacterial activity. This can be conveniently inverted by a version of the Mitsonobu reaction in which hydroxide is used as the displacing nucleophile; there is thus obtained the intermediate (**11-12**).
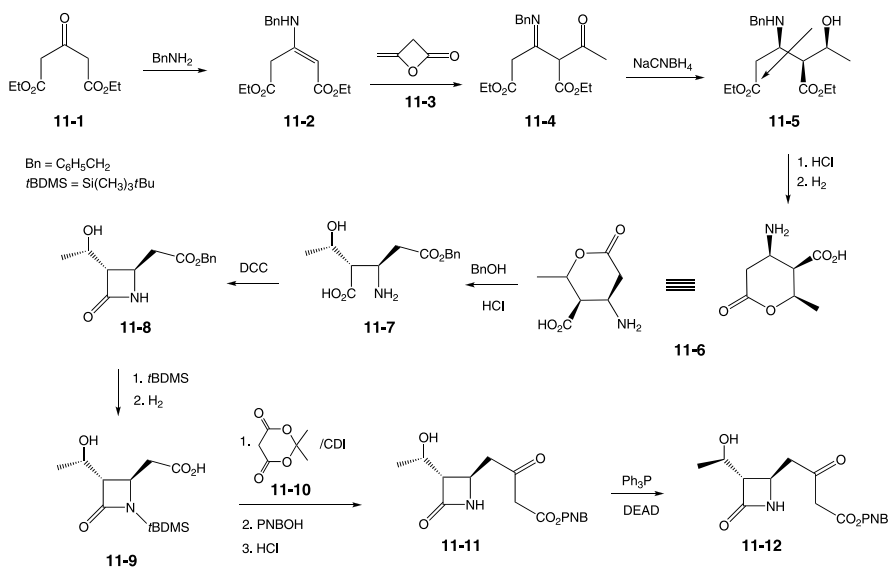
One of the key steps in building the fused ring involves the reaction of the activated acetoacetate methylene group in that compound with toluenesulfonyl azide to give the diazo intemediate (**12-1**). Treatment of that product with rhodium acetate leads to a loss of nitrogen with the consequent formation of carbene (**12-2**); this inserts into the adjacent amide N—H bond to form a five-membered ring and thus the carbapenem (**12-3**) [15]. The first step in the incorporation of the thioenol function consists in the conversion of the ketone to the enol phosphate derivative

(**12-4**) by reaction with diphenyl chlorophosphate. The cystamine amidine required for the next step cannot be used as such as it spontaneously cyclizes to a thiazoline. The silyl ether avoids that side reaction; thus, treatment of (**12-4**) with the silyl amidine (**12-5**) leads to the thioenol ether (**12-6**) by addition-elimination. Removal of the protecting groups by sequential acid and base hydrolysis gives (**12-7**) as a racemate [16]. The chiral product **imipenem** can be obtained by the same scheme using a resolved intermediate.
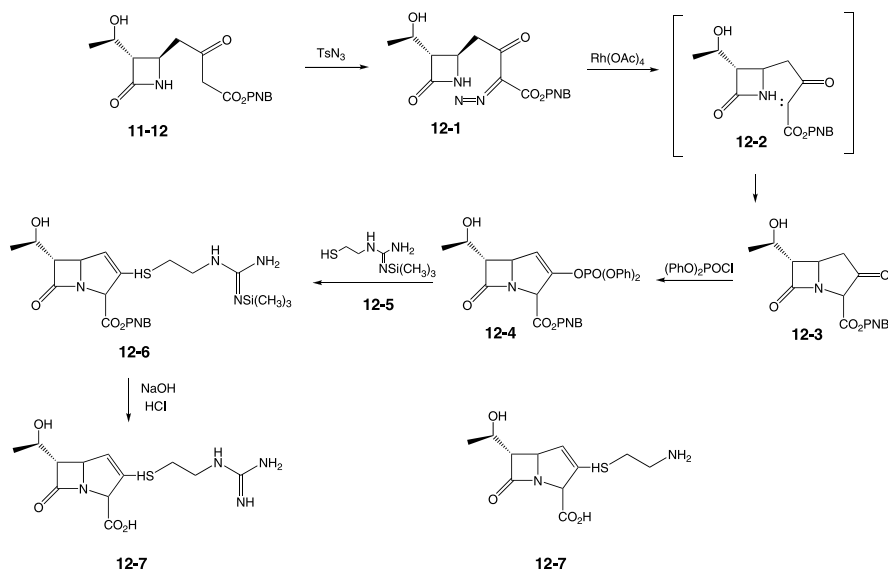
The enol phosphate (**12-4**) proved to be a versatile intermediate for the preparation of other penem antibiotics. Thus reaction of this derivative with pyrrazolidine (**13-1**)
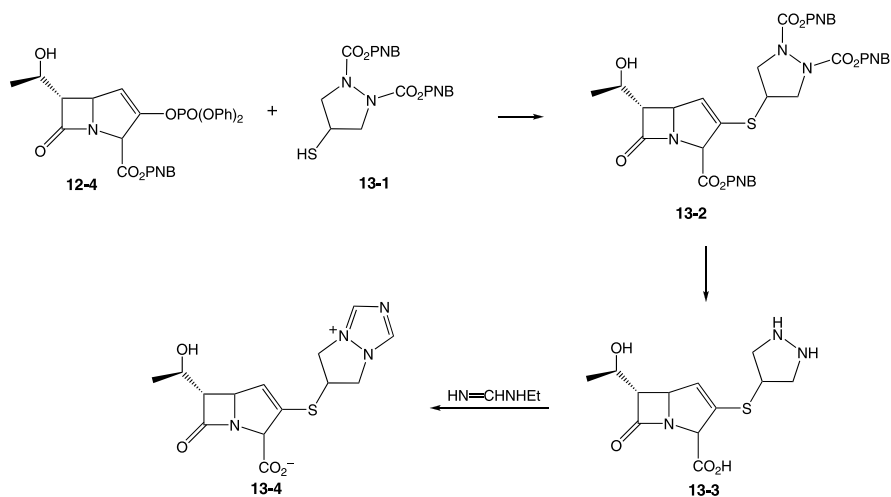
leads, as above, to the displacement of the enol phosphate by more nucleophilic sulfur and the formation of the enol sulfide (**13-2**). The protecting groups are next removed to afford the cyclic hydrazine (**13-3**). Treatment of this product with ethyl formidate leads to the conversion of that function to a fused 1,2,4 triazole ring. The first-formed product is then passed through an ion exchange column to convert it to a betaine, affording the antibiotic **biapenem** (**13-4**) [17].

The side chain of a related penem comprises a heterocyclic ring derived from proline. Preparation of the side starts by reaction of proline itself (**14-1**) with *para*-nitrobenzyloxycarbonyl chloride to form the corresponding carbamate. The sodium salt of the carboxyl is then alkylated by means of dianisylmethyl chloride (**14-2**). Mitsonobu reaction of that intermediate with a thioacetic acid in the presence of triphenylphosphine and DEAD leads to the replacement of the ring hydroxyl by sulfur with an inversion of the configuration (**14-3**). Treatment of this product with trifluoroaceric acid cleaves the dansyl ester. The resulting free acid is then activated as its mixed anhydride. That leads to the amide (**14-4**) on treatment with dimethylamine; this is converted to the free thiol by saponification. Reaction of this last intermediate with the penem (**14-6**) leads to the replacement of the phosphate by sulfur on the pyrrolidine ring (**14-7**). Hydrogenolysis of the *para*-nitrobenzyl groups then affords the penem antibiotic **meropenem** (**14-8**) [18].
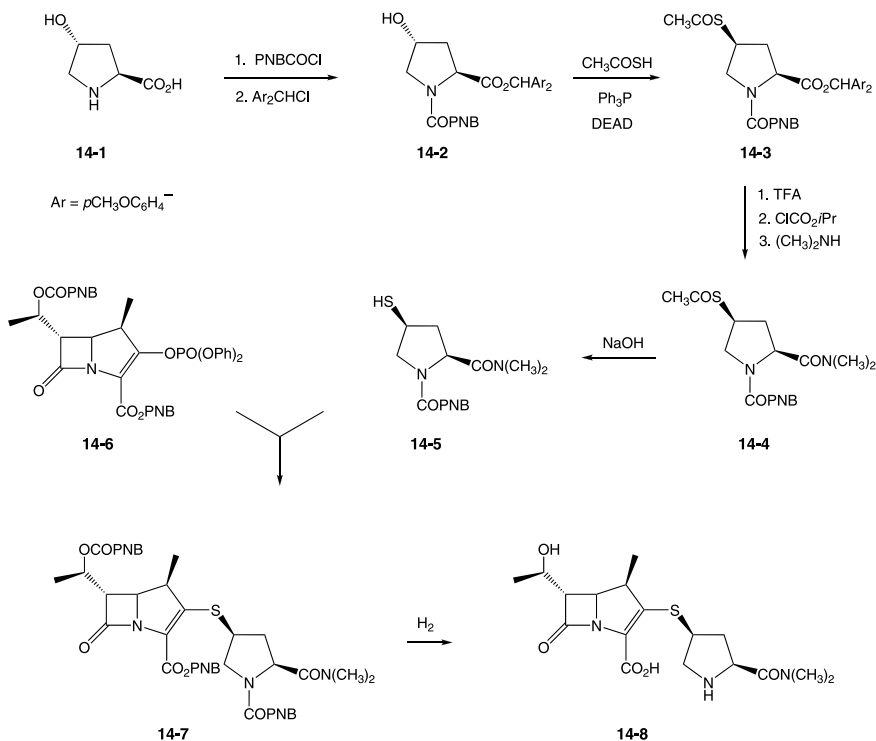
There is arguably no more vivid example of the validity of Darwinian evolution than the emergence of strains of bacteria resistant to classes of antibiotics. Pathogenic bacteria that are resistant to several classes of drugs, the multidrug resistant organisms, are of particular concern. The enol phosphate penem (**15-9**) provides access to a beta lactam active against such pathogens. Preparation of the side chain starts with the protection of nitrogen of hydroxyproline (**15-1**) as its diisopropyl phosphoryl derivative (**15-2**). The carboxyl is then activated as the mixed anhydride (**15-3**) by reaction with diphenylphosphinic anhydride. The ring hydroxyl is next converted to its mesylate (**15-4**) by reaction with methanesulfonyl chloride. Treatment of that intermediate with sodium sulfide serves to replace the phosphorus on the carboxyl group by sulfur to afford the thioacid anion (**15-5**). Under the somewhat basic reaction conditions the sulfide anion slowly displaces the transannular mesylate group to form a bridged thiolactone ring. The stereochemistry at the new carbon sulfur bond is inverted in the process (**15-6**). That intermediate is then treated with 3-aminobenzoic acid (**15-7**). The thiolactone now opens to form amide (**15-8**), thus completing the side chain. Reaction of commercially available enol phosphate (**15-9**) with the side chain intermediate (**15-8**) leads to the replacement of the phosphorus by the side chain thiol function. Removal of the protecting groups then affords the carbapenem **ertapenem** (**15-10**) [19].
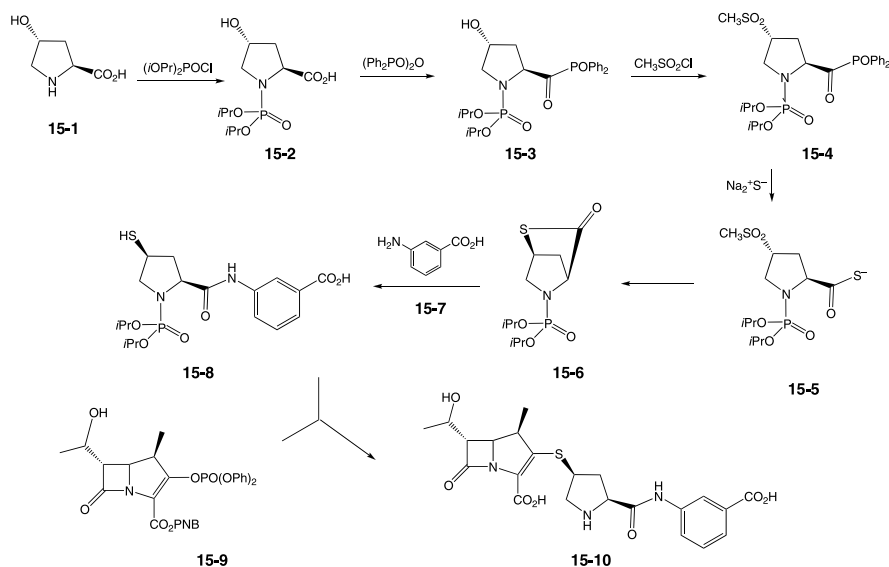
The cyclization of 1,5-dicarbonyl chains by means of the deoxygenating reagent triethyl phosphite provides an alternate strategy for building the fused five-membered penem ring. The first example in fact actually comprises a 1,5-oxa-thio array. Reaction of the perhydrothiophene oxide (**16-1**) with the anion from carbon disulfide

and sodium isopropoxide leads to the displacement of the tosylate and the formation of the salt (**16-2**) with an inversion of the configuration. Treatment of that product with the azetidone (**16-3**) leads to the replacement of the acetoxyl next to nitrogen, in this case with retention of the configuration (**16-4**). This result can be rationalized by assuming an initial loss of the acetoxyl to form a carbocation; this would then capture sulfur from the more open side. The amide nitrogen is next acylated with half-acid chloride from allyloxy oxalate ester to afford (**16-5**). The key step then involves the cyclization of the 1,5 di(thia)carbonyl array by means of triethyl phosphite to yield the penem (**16-6**). Removal of the silyl protecting group on the side chain by means of a fluoride ion followed by the removal of the allyl ester with complexed palladium then affords the antibiotic **sulopenem** (**16-7**) [20].
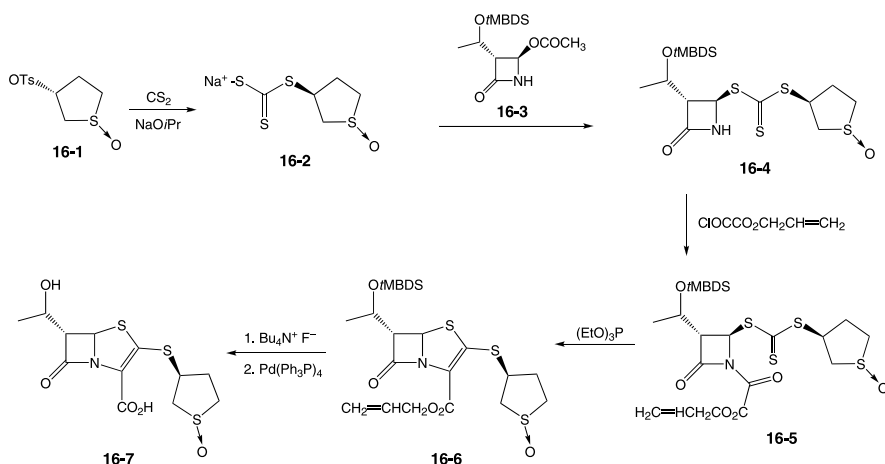
Fusing an additional ring onto the penem nucleus leads to an antibiotic that is active against a broad spectrum of bacteria. The scheme used to prepare the compound involves much the same strategy as the foregoing example in that the key step again involves a triethylphosphite induced ring formation. Activation of the future additional fused ring starts by the formation of the silyl enolate (**17-2**) by reaction of chiral metoxycyclohexanone (**17-1**) with trimethylsilyl trifllate. Treatment of that intermediate in turn with methyl lithium and then zinc bromide affords the zinc reagent (**17-3**). Reaction with the familiar azetidone (**16-3**) leads to the displacement of the acetoxyl; the apparent front-side displacement can be rationalized much as in the preceding case. The product from that reaction (**17-4**) is next converted to the oxalic acid derivative (**17-5**) by reaction with the same half-acid chloride. Deoxygenation of the 1,5-dicarbonyl array using triethyl phosphate then closes the ring to afford the penem (**17-6**). Sequential treatment with fluoride ion followed by complexed palladium removes the protection groups. There is thus obtained the penem **sanfetrinem** (**17-8**) [21].
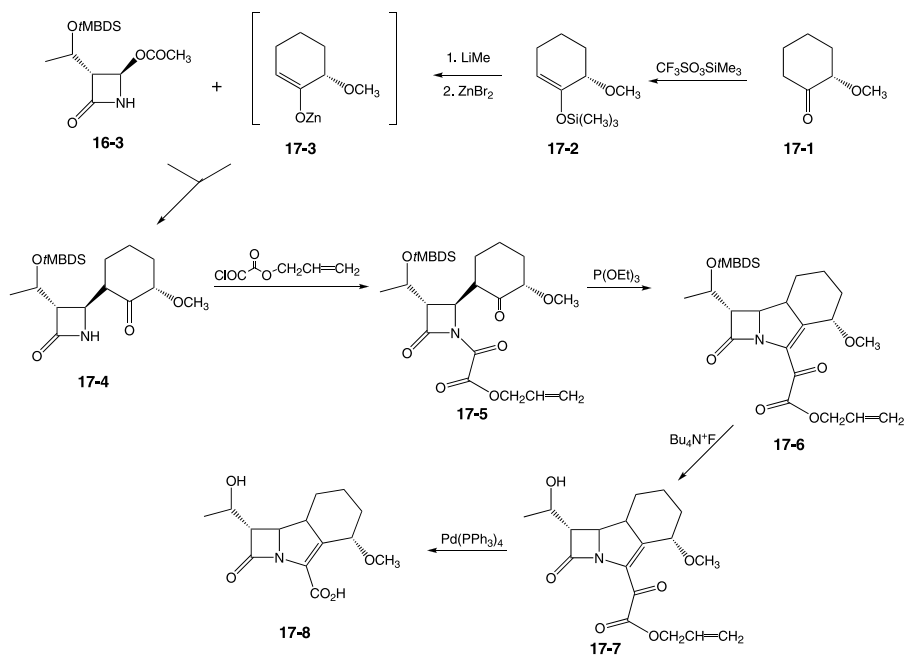
14.2. CEPHALOSPORINS

Not too long after the widespread adoption of penicillin for the treatment of bacterial infections, a related beta lactam compound was isolated as a consequence of the continuing search for new drugs. This compound, cephalosporin C (**18-1**), differs in that a six- rather than a five-membered ring fused onto the azetidone. Though the agent showed superior resistance to the beta lactamases that destroy this class of antibiotics and a broader spectrum of action than penicillin, its clinical use was precluded by its low potency and poor biopharmaceutical properties. The development of a method for efficiently removing the aminoadipate side chain provided the first method for preparing 7-aminocephalosporanic acid, 7-ACA (**18-4**), which serves the same role in this series as does 6-APA (**2-4**) in the penicillin series. (Attempts to remove the side chain directly yield less than 1% 7-ACA.)

The key reaction, based on a method for removing glutamate residues in peptides, involves the conversion of the sole primary amine in the molecule to a diazo function. The most expeditious method consists of reacting (**18-1**) with nitrosyl chloride. The resulting diazo function in the product (**18-2**) can be displaced formally by oxygen from the enol form of the amide at the 7 position to form the iminolactone (**18-3**); the reaction may involve a spontaneous loss of nitrogen followed by capture of the resulting carbocation. Hydrolysis of the imine function in the product the leads to one of the key intermediates in this series, 7-ACA (**18-4**) [22].
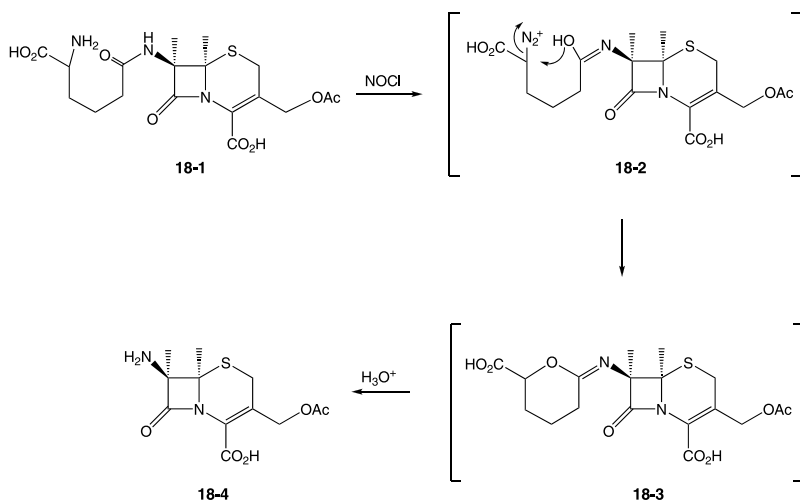
This intermediate, like 6-APA, incorporates a primary amine that can be coupled with a host of side chains. The presence of an additional reactive function, the allylic acetate at the 3 position, provides an additional center that can be modified. The observation that both types of modifications provided improved antibiotics has resulted in the synthesis of hundreds of analogues. The very few examples discussed below barely scratch the surface in this field. One of the earliest examples of a doubly derivatized 7-ACA derivative, **cephalothin** (**19-1**), is still widely used as an antibiotic. Acylation of (**18-4**) with 2-thiophenylacetyl chloride gives the corresponding amide (**19-2**). Heating that product with pyridine leads to the displacement of the allyl acetate by the basic nitrogen. The resulting product, **cephalothin** (**19-3**), is isolated as the internal betaine [23].
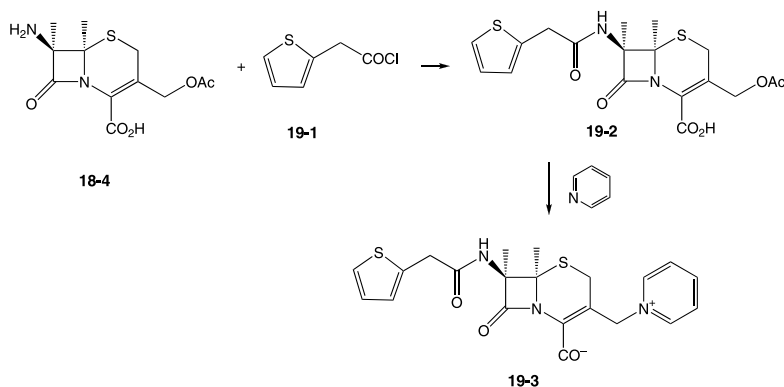
The order of the steps can be reversed. Thus, reaction of (**18-4**) with the tetrazole-thione (**20-1**) results in the displacement of the allylic group by nucleophilic sulfur

and the formation of the intermediate (**20-2**). This product is then acylated with acid chloride from the dichoroacetyl ester of D-madellic acid to provide amide (**20-3**). The protecting group on the side chain is then removed by reaction with zinc metal to give the antibiotic **cefamandole** (**20-4**) [24].
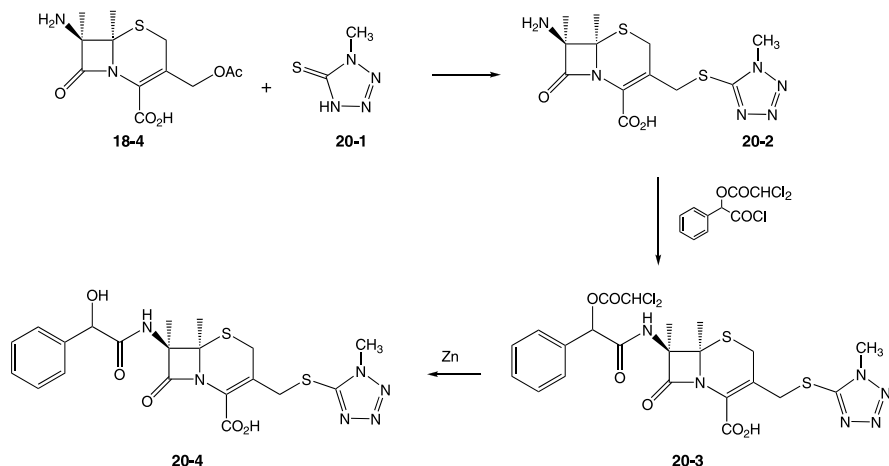
The incorporation of complex side chains at the 7 position based on alkyloximes of 2-amino-thiazole-5-gyloxylamides has provided drugs with very wide antibacterial activity that extend to hitherto resistant species such as *pseudomonas*. The preparation of one of the simpler side chains involves, first, the formation of the methyl ether from the oxime obtained by the nitrosation of methyl acetoacetate. Chlorination of the product, for example with sulfuryl chloride, gives the intermediate (**21-1**). The aminothiazole ring is then formed by reaction of that with thiourea to give (**21-2**). The free acid (**21-3**) is obtained by saponification of the product. The protected acid chloride (**21-5**) is obtained by sequential acylation of the amino group with chloroacetyl chloride and then reaction with thionyl chloride.
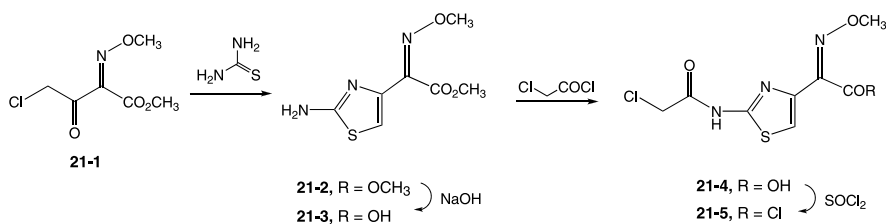
In a typical example of the synthesis of one of these broad-spectrum agents, the cefamandole intermediate (**20-2**) is first acylated with the protected thiazole acid chloride (**21-5**) to give the amide (**22-1**). Removal of the protecting group by reaction of that intermediate with thiourea can be envisaged as involving an initial displacement of chlorine on the side chain by sulfur to form an intermediate such

as (**22-3**); this then cyclizes to a second thiazole ring in the process cleaving the protecting group. There is thus obtained **cefmenoxime** (**22-2**) [25].
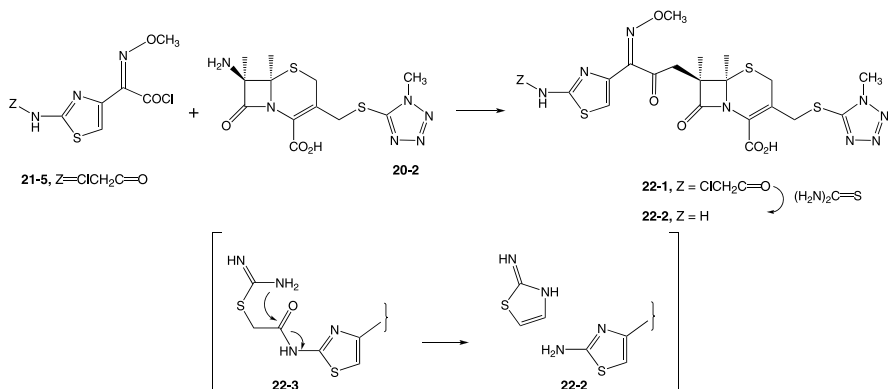
The presence of an internal salt, a zwitterion or betaine, in cephalosporins enhances their solubility in water, making such agents particularly suitable for parenteral administration. The preparation of one such drug first involves the replacement of allyl oxygen in the *tert*-butylcarbonyloxy protected 7-ACA derivative (**23-1**) by nitrogen in azaindan (**23-2**) to afford the betaine (**23-3**). The protecting group is then removed so as to free the amine on the azetidone (**23-4**) by treatment with trifluoroacetic acid. Reaction with the thiazole free acid (**23-5**) in the presence of DCC then affords **cefpirone** (**23-6**) [26].
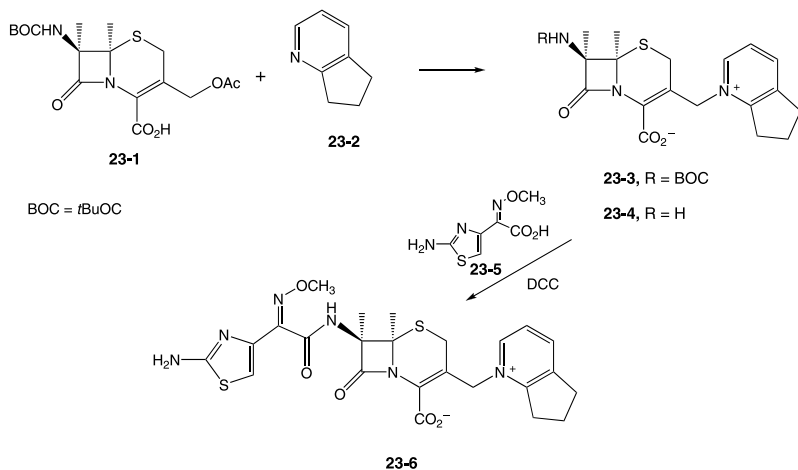
The order of those steps can be reversed. The synthesis of the homologous compound **cefquinome** (**24-6**) starts by protecting the carboxyl group in cefotaxime (**24-1**), itself a potent antibiotic as its silyl ester (**24-2**), by reaction with

trimethylsilyl-*N*-methyltrifluoroacetamide. The allylic acetate is then replaced by iodine by means of trimethylsilyl iodide (**24-3**). That intermediate is then allowed to react with 5,6,7,8-tetrahydroquinoline (**24-4**) to afford the quaternary salt (**24-5**). The silyl ester is then cleaved with aqueous acid. Adjustment of the pH then gives the betaine cephalosporin cefquinome (**24-6**) [27].
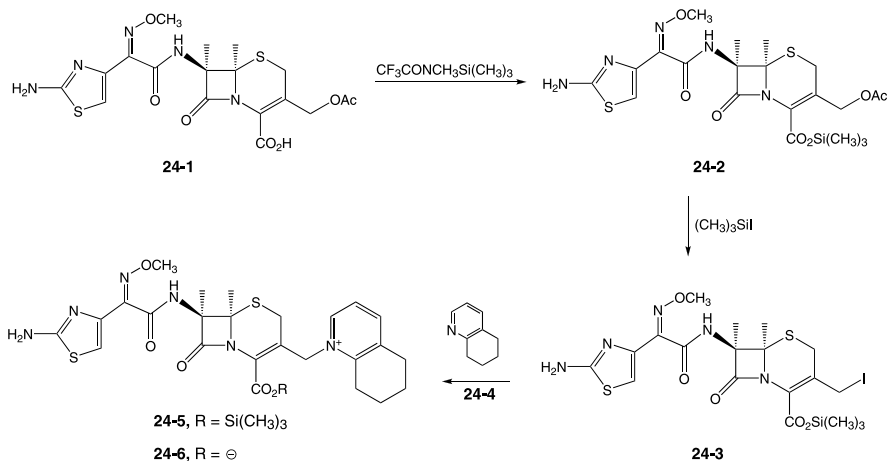
Acylation of the amino group at position 7 markedly enhances the oral absorption of beta lactam antibiotics. The key step in the synthesis of these compounds is of course quite analogous to peptide coupling; the mixed anhydride method has been used extensively for preparing compounds in this series. Thus, reaction of 7-ACA (**18-4**) with the mixed anhydride from the *tert*-BOC derivative of D-phenylglycine and *iso*-butyl chloroformate (**25-1**) leads to the amide (**25-2**). Treatment of the product with trifluoroacetic acid leads to the free amine and thus **cephaloglycin** (**25-3**) [28]. An increase in lipophilicity, by deleting the acetoxy group at position 3, further improves oral availability with no loss in antibiotic activity. Catalytic reduction of (**25-3**) over palladium on charcoal leads to the hydrogenolysis of the allylic acetoxy group. There is thus obtained the widely used antibiotic **cephalexin** (**25-4**) [29].
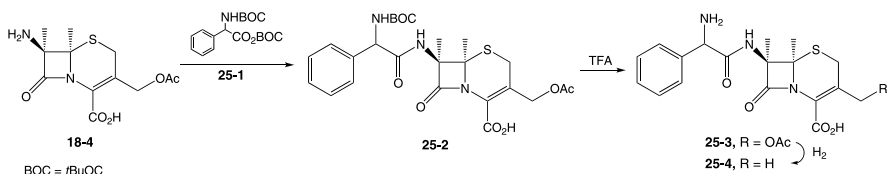
Benzyl penicillin (**1-1**) and penicillin V (**26-1**), as has been noted earlier, are now available in virtually tonnage quantity. The observation that these compounds sometimes occur together with cephalosporins, combined with the fact that the latter may be viewed as a dehydro form of their five-membered counterparts, led to speculation that the antibiotics might be formed by a common pathway. The chemical work

occasioned by this theory led to several efficient routes for the preparation of cephalosporin starting materials from penicillins [30]. In its simplest application, (**26-1**) is first oxidized to the corresponding sulfoxide (**26-2**). Treatment of that compound with toluenesufonic acid in refluxing xylene leads to a ring opening to the sulfenic acid intermediate (**26-3**). This cyclizes under reaction conditions with a loss of oxygen by addition to the conjugated double bond to afford the cephalosporin (**26-4**) [31]. The phenoxyacetamido side chain is then removed via its imino chloride by the same sequence of steps used for removing the phenylacetamide side chain in penicillin (**2-1 → 2-4**) to give 7-aminodeacetylcephalosporanic acid (7-ADCA) (**26-6**).
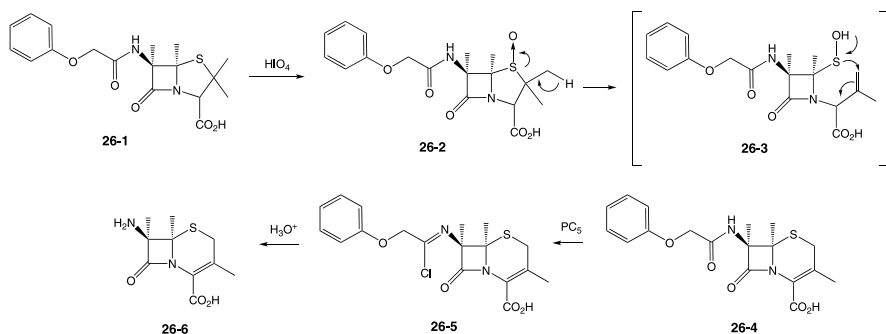
The deacetyl compound (**26-6**) is now used for the direct production of **cephalexin** (**25-3**) as well as several other related agents that incorporate similar amide side chains. For example, reaction of the protected 7-ADCA derivative (**27-2**) with the *tert*-BOC amide from D-*para*-hydroxyphenylglycine (**27-1**) by the mixed anhydride method gives the amide (**27-3**). Serial scission of the *tert*-BOC group and the silyl ester affords the antibiotic **cefadroxil** (**27-4**) [32]. Exactly the same sequence starting

with the Birch reduction product from D-phenylglycine (**27-5**) leads to **cephradine** (**27-6**) [33].

Acylation of the amine with the methoxime from aminothiazole-glyoxylate has a similar effect on broadening the antibacterial spectrum in the 3-methyl series. In this case, the amine group on the starting thiazole (**21-3**) is first protected by conversion to (**28-2**) by alkylation with thriphenylmethyl chloride. Condensation of the acid by the mixed anhydride method with 7-ADCA (**26-6**) leads to the corresponding amide. The trityl group is then removed to afford the antibiotic **cefetamet** (**28-3**) [34].

21-3   **28-1**, R = CH₃   **28-2**, R = H   **26-6**

28-3

Considerable freedom exits as to the nature of the substituent on the six-membered ring. Good antibiotic activity is retained when the methyl or acylmethyl of the more common agents is replaced by vinyl. Displacement of the vinylic chloride in cephalosporin (**29-1**) by triphenylphosphine yields the corresponding phosphonium salt (**29-2**). A strong base converts that, as in the case of simpler compounds, to the ylide. Treatment with propionaldehide then affords the vinyl derivative as a mixture of geometric isomers (**29-3**). Removal of the protecting groups leads to the antibiotic **cefprozil** (**29-4**) [35].

29-1   **29-2**

1. Base
2. CH₃CH₂CH=O

29-4   **29-3**

The synthesis of the vinyl antibiotic **cefdinir**, which starts with the preformed unsaturated nucleus (**30-2**), illustrates a scheme that builds the almost obligatory aminothiazole *in situ* as the last step. Acylation of the amino group in (**30-2**) with 3-bromoacetoacetic acid (**30-1**) leads to the amide (**30-3**). Reaction of that intermediate with sodium nitrite proceeds on the activated methylene to form the nitrite as the initial product. This spontaneously tautomerizes to the observed oxime (**30-4**). Treatment with thiourea, in one of the standard procedures for forming thiazoles, then leads to (**30-5**). There is thus obtained cefdinir (**30-5**) [36].
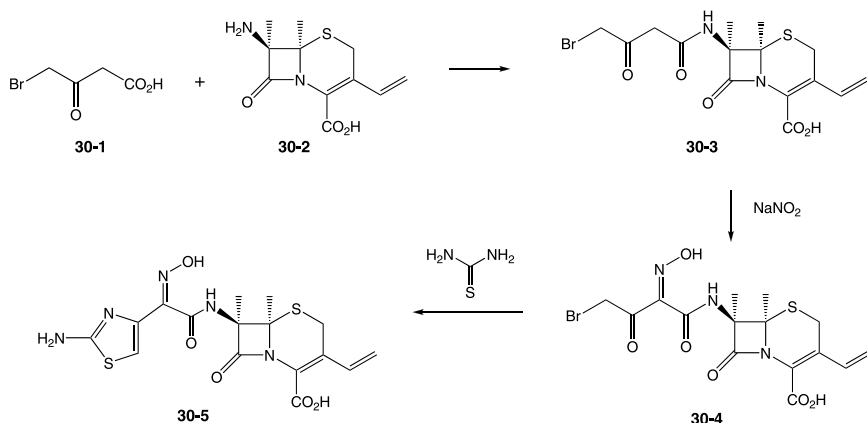
The modified cephalosporin **ceftobiprole** (**31-8**), yet another compound that contains a double bond at the ring carbon, though in this case with a rather complex extended side chain, has shown activity in the clinic against some strains of multidrug resistant bacteria. The synthesis starts with the well-precedented acylation of the cephalosporin (**31-2**), available in several steps from the commercially available 7-acetoxy cephalosporanic acid, with the activated thiadiazole carboxylic acid (**31-1**). The hydroxyl group in the product (**31-3**) is then oxidized with manganese dioxide to afford the corresponding aldehyde (**31-4**). This product is then condensed with the *bis*-pyrrolidyl phosphonium salt (**31-5**), itself protected with the
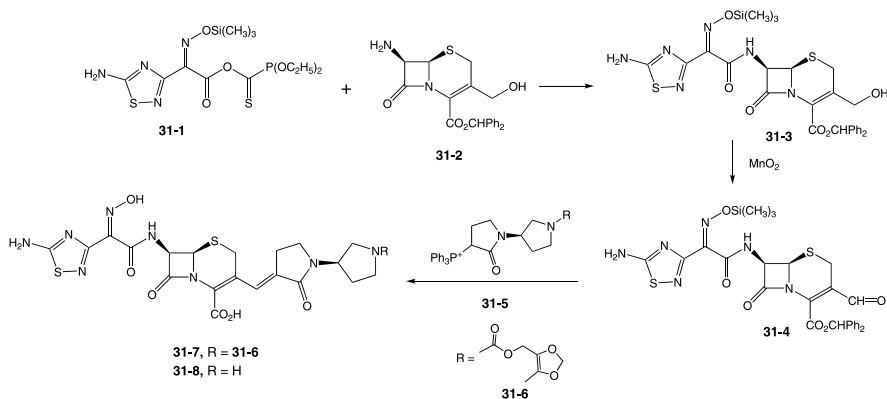
complex carbonate (**31-6**). Removal of the several protecting groups from (**31-7**) then affords the highly modified cephalosporin ceftobiprole (**31-8**) [37].

Very good antibiotic activity is, interestingly, retained when the substituent at the 3 position comprises a heteroatom or even hydrogen. The preparation of these compounds relies on the chemistry involved in the penicillin to cephalosporin ring enlargement sequence noted previously. One synthesis for the drug in which the 3-substituent consists of chlorine, **cefaclor** (**32-9**), starts with the sulfoxide (**32-1**) of penicillin V protected as its *para*-nitrobenzyl ester. Reaction of that compound with a chlorinating agent such as *N*-chlorosuccinimide in the presence of an acid scavenger probably first involves chlorination on sulfur to form a chlorosulfonium chloride species; this then ring opens with a loss of hydrogen chloride to the unsaturated sulfenyl chloride (**32-2**). Treatment of that intermediate with a Lewis acid then leads to a Friedel–Crafts-like attack on the olefin to afford the cyclized product; the double bond concomitantly shifts to the exocyclic position to give (**32-3**). Ozonization in the cold followed by cleavage of the ozonide affords the corresponding ring ketone; this exists virtually entirely as its conjugated enol (**32-4**). The sulfoxide is then reduced to afford the cephem (**32-5**). The phenoxyacyl side chain is then removed by the usual sequence. The reaction of this intermediate with phosphorus pentachloride transforms the side chain amide to its imino chloride and at the same time converts the ring enol to the enol chloride. The former hydrolyzes on workup to afford the primary amine to give (**32-6**). That product is then converted to the corresponding amide with D-phenylglycine (**32-7**) by a standard scheme, using a mixed anhydride coupling of *t*-BOC protected amino acid (**32-8**). Sequential removal of the BOC protrecting group followed by hydrolysis of the ester then gives **cefaclor** (**32-9**) [30].
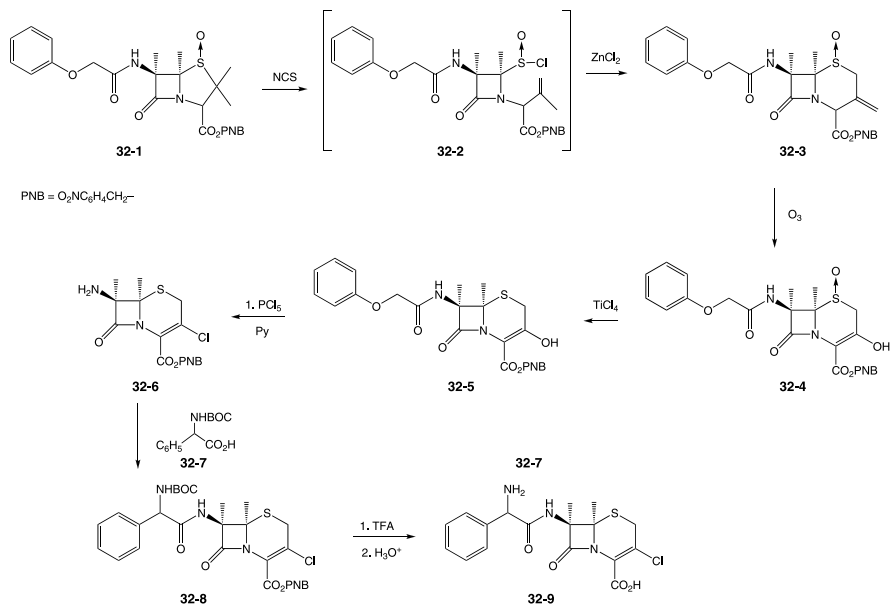
An enol such as (**32-5**) can in principle serve as the intermediate for the antibiotic **cefroxadine** (**33-9**), in which the substituent at the 3 position consists of a methyl ether. The route differs from that above in that the key step involves a ring opening of penicillin sulfoxide by mercaptobenzo-thiazole (**33-2**). Application of that reaction was discussed earlier in connection with the synthesis of the beta lactamase inhibitor **tazobactam** (**10-10**). In the present case, the action of that reagent on the benzhydryl ester (**33-1**) of penicillin V sulfoxide affords the ring opened intermediate (**33-3**). The superfluous carbon is next removed by ozonization to afford the corresponding β-ketoester (**33-4**), which again exists mainly as the enol. This is next converted to its methyl ether (**33-5**) by treatment with diazomethane. The reaction of this last intermediate with the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can be envisaged as involving first the formation of a carbanion on the terminal methyl group; this then attacks the disulfide with expulsion of the excellent leaving group, benzothiazolomercaptide. There is thus formed the 3-methoxy cephem (**33-6**), which still however bears the penicillin V side chain. That is then removed by the standard imino chloride route to give the key intermediate (**33-7**). The free amine at the 7 position is then acylated in the standard fashion with the *t*-BOC derivative from (2,5-dihydrophenyl)glycine (**32-7**). Removal of the protecting groups from (**33-8**) leads to the antibiotic **cefroxadine** (**33-9**) [38].
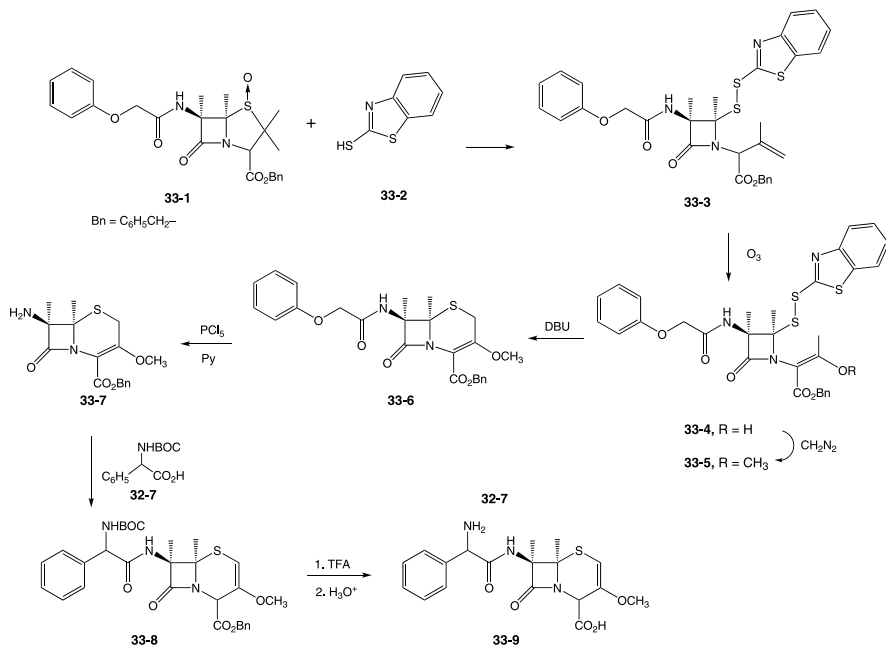
The enolic chlorine at the 3 position in (**32-6**) can be removed under reductive conditions such as zinc and acid to give the cephem (**34-1**) that now

bears hydrogen at that position. Acylation of this compound with the acid chloride from the aminotiazole intermediate (**23-5**) affords the antibiotic **ceftizoxime** (**34-2**) [39].
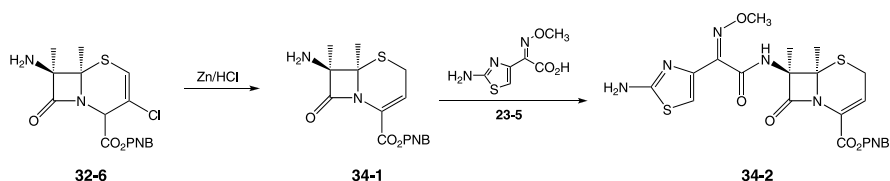
The cephamycins comprise a set of beta lactamase resistant fermentation products that consist of cephalosporins that include a methoxy group on the carbon bearing the amine. These agents were not suitable as drugs in their own right because of their poor biopharmaceutical properties. This was due to the circumstance that the natural products, like the original cephalosporins, occurred as their highly
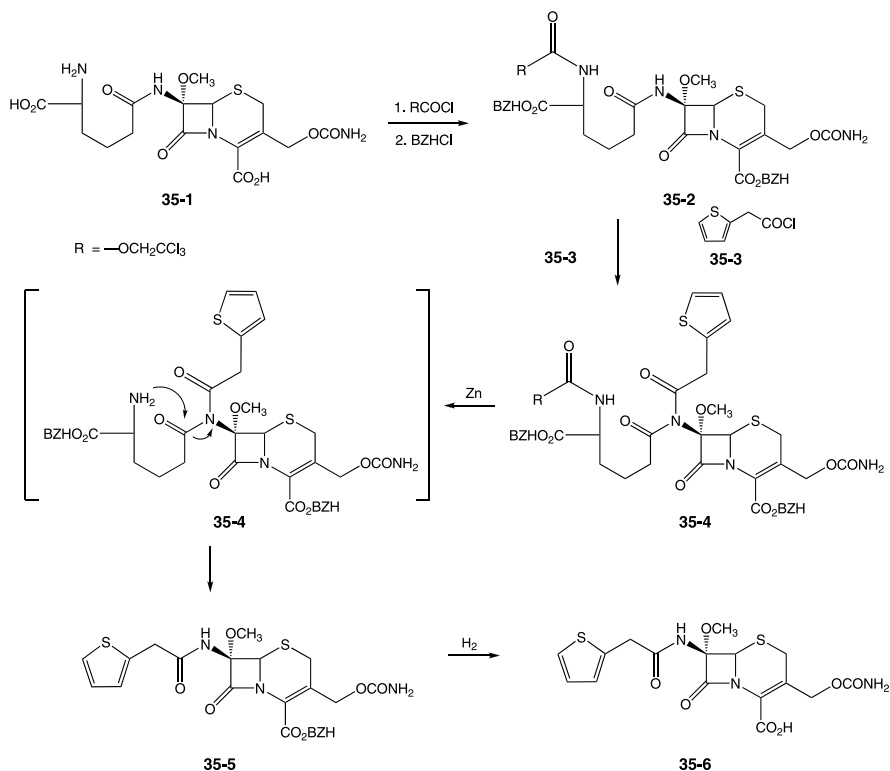
polar aminoadipic acid amides. A number of methods were elaborated for the direct introduction of the methoxyl group in the course of the search for an analogue suitable for use in the clinic. These are generally similar in concept to that discussed above in connection with the 6-methoxy penicillin **temocillin** (**8-8**). A method for the direct exchange of side chains was developed when amide with 2-(2-thienyl)-acetic acid was identified as the clinical candidate. The preparation starts with the acylation of the primary side chain amine in cephamycin C (**35-1**) with tricholro-ethoxycarbonyl chloride; reaction of the product with benzhydryl chloride and a base converts both carboxylic acids to their benzhydryl esters to give (**35-2**). This intermediate is then treated with 2-(2-thienyl)acetyl chloride (**35-3**) in the presence of trimethylsilyl trifluoroacetamide to add the second amide on the amine at 7 to afford the reactive imide (**35-4**). The trichloroethyl carbamate group is then very selectively cleaved by reaction with zinc metal. The newly liberated primary side chain amine in this transient intermediate (**35-4**) then reacts with the adipyl amide carbonyl and in effect displaces the side chain (**35-5**). Hydrogenolysis of the benzhydryl ester affords the antibiotic **cefoxitin** (**35-6**) [40].

The compounds obtained by the replacement of ring sulfur by carbon, as in the case of penicillins, show somewhat improved antibiotic properties. A free radical—based route has been described for the conversion of fermentation derived cephalosporins to their carbocyclic derivatives. The first step in this sequence consists of the condensation of the cephalosporin sulfone (**36-1**) with formaldehyde and dimethylamine; the initial product from the Mannich-like reaction consists of the exomethylene derivative at the position adjacent to the activating sulfone. The product is treated *in situ* with phenylselenol to give the Michael adduct (**36-2**). This fragments with an extrusion of sulfur dioxide when heated with the free radical initiator AIBN in the presence of tributyltin hydride; the reaction can be envisaged as leading to the
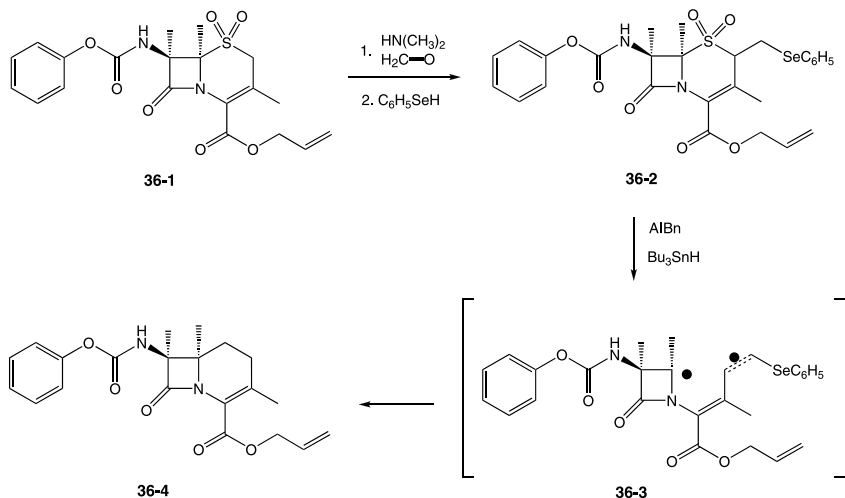
formation of a di-radical such as (**36-3**). The radical on the newly formed side is presumably in equilibrium with that next to selenium. This can then close to a six-membered ring; reductive loss of phenylselenol affords the observed carbacephem (**36-4**) [41].

The key sequence in a somewhat involved stereospecific total synthesis of a carbacephem starts by preparation of a chiral auxiliary. It is interesting to note that nitrogen is the only atom from this molecule retained in the final product. Construction of this moiety starts with the formation of the carbethoxy derivative (**37-2**) from L(+)-phenylglycine (**37-1**). Selective reduction of the free carboxyl group with borane. THF leads to the hydroxycarbamate (**37-3**). In a one-pot sequence, this is first cyclized to the corresponding oxazolidinone (**37-4**) by means of sodium hydride and then alkylated with ethyl bromoacetate (**37-5**). Saponification of the side chain then affords the chiral acetic acid (**37-6**). The carboxyl group is then activated by conversion to its acid chloride (**37-7**).
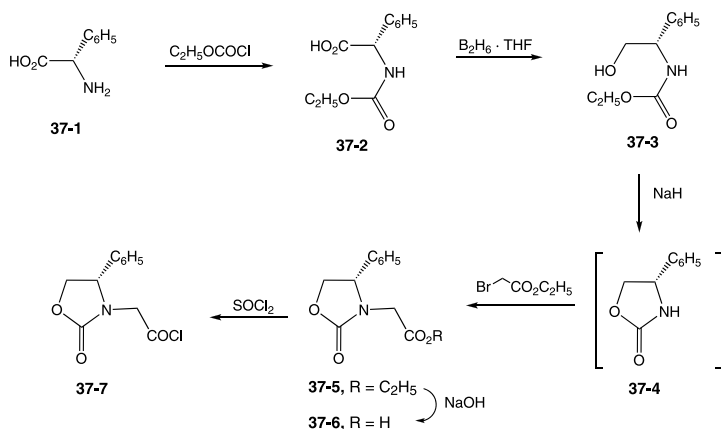
The beta lactam moiety is formed by the 2+2 cycloaddition of a ketene with an imine. Thus reaction of the acid chloride (**37-7**) with the benzylimine from 3-furylacrolein (**38-2**) in the presence of triethylamine goes directly to the azetidone (**38-3**),
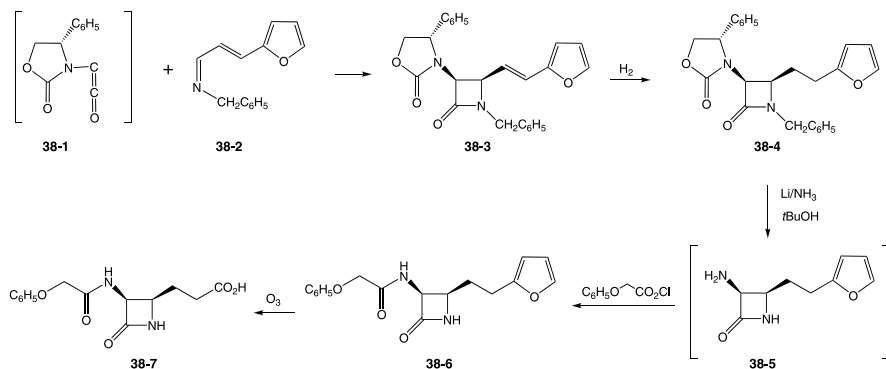
in all probability via the ketene (**38-1**). The reaction is remarkably stereoselective, giving the desired diastereomer in a ratio of 92 : 8. The double bond is then reduced by catalytic hydrogenation to give (**38-4**). Birch reduction using lithium in liquid ammonia with *tert*-butanol as a proton source cleaves both benzylic amine bonds; the benzyl protecting is thus lost directly while the oxazolidinone first opens to a carbamate that is cleaved under reaction conditions. This then affords the bare azetidone (**38-5**). The primary amine is then protected on an interim basis as its phenoxyacetamide (**38-6**) by reaction *in situ* with phenoxyacetyl chloride. Furyl groups are well-precedented latent carboxylic acids. Thus, ozonization of that moiety in (**38-6**) gives the corresponding acid (**38-7**) on oxidative workup of the ozonide.

The strategy for building the fused six-membered ring echoes that used for the synthesis of **imipenem** (**12-6**), though the reagents differ significantly. Extension of the side chain that will form the new ring starts by activation of the terminal acid as its imidazolide by reaction of the acid (**38-7**) with carbonyl diimidazole. This is then used to acylate the magnesium salt for the mono-*para*-nitrobenzyloxy ester of malonic acid. The resulting β-tricarbonyl compound decarboxylates on workup to afford the keto-ester (**39-1**). This is then diazotized with *para*-dodecylphenylsulfonyl azide (DSO$_2$N$_3$) to afford the intermediate (**39-2**). Treatment of the diazo compound with rhodium tetraoctanoate leads to the formation of the carbene by a loss of nitrogen. This reactive species inserts into the amide N—H bond to form a fused piperidone ring; the product exists largely as its enol tautomer, as in the case of the analogous cephem (**39-3**). The phosphorus pentachloride commonly used for the next step is replaced in this case by dichlorotriphenyl phosphite; reaction with that reagent converts the enol to its chloride and serves to remove the amide at the 7 position via its imino chloride. There is thus obtained the primary amine (**39-4**). The D-phenylglycine side chain is then incorporated by the usual sequence using, in this case, the aminoacid as its ethyl acetoacetate eneamine. The ester is then removed by treatment with zinc; exchange of the eneamine with semicarbazide then removes that protecting group to afford **loracarbef** (**39-5**) [42].
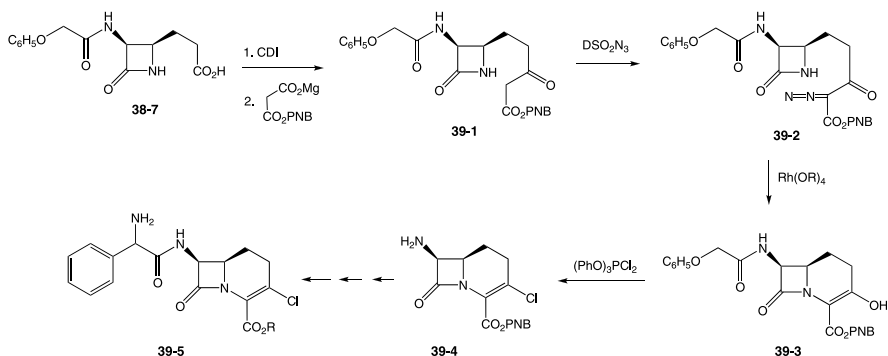
14.3. MONOBACTAMS

The soil screening programs prompted by the discovery of penicillin and streptomycin led to the finding of many new classes of antibiotics beyond the beta lactams discussed in this book. The great majority of those agents are elaborated as chemical defenses by molds and actinomycetes. The search for new antibiotics turned to other sources as the soil screening programs started yielding diminishing returns. This led to the discovery of a promising antibacterial agent that was itself produced by the bacterium, *Chromobacterium violaceum*. Structural determination revealed that this agent surprisingly consisted of the unfused azetidone (**40-10**). The natural product, as has often been the case in the beta-lactam series, was again not suitable as a drug per se.

One of the first compounds to be introduced to the clinic, **aztreonam** (**40-9**), has been produced by total synthesis. Construction of the chiral azetidone starts with amide formation of L-threonine (**40-1**) via its acid chloride; treatment with ammonia leads to the corresponding amide (**40-2**). The primary amino group in that product is then protected as its carbobenzyloxy derivative (**40-3**). Reaction of that product with methanesulfonyl chloride affords the mesylate (**40-4**). Treatment of that intermediate with the pyridine sulfur trioxide complex leads to the formation of the *N*-sulfonated amide (**40-5**). Potassium bicarbonate is sufficiently basic to ionize the very acidic proton on the amide; the resulting anion then displaces the adjacent mesylate to form the desired azetidone; the product is isolated as its tetrabutyl ammonium salt (**40-6**). Catalytic hydrogenation over palladium removes the carbobenzyloxy protecting group to afford the free primary amine (**40-7**). The
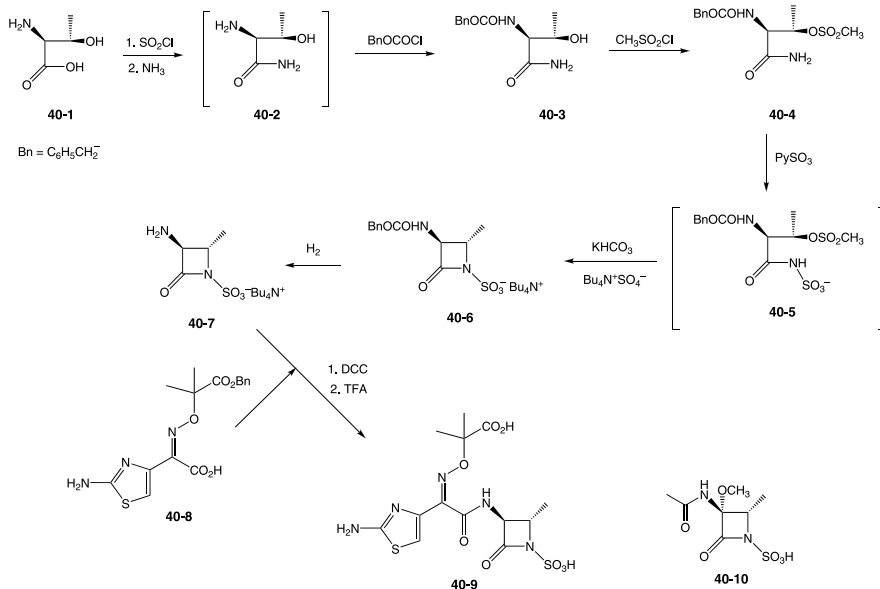
side chain in this compound mirrors those used in some of the more complex cephalosporins. Thus, reaction of the primary amino group in (**40-7**) with the half-ester (**40-8**) in the presence of dicyclohexyl carbodiimide (DCC) affords the corresponding amide. The protecting group on the side chain is then removed by treatment with trifluoroacetic acid to afford **aztreonam** (**40-9**) [43].

The configuration of the carbon bearing a carbamate in the monobactam, **carumonam** (**41-9**), is interestingly the reverse of that in the natural product or in **aztreonam**. The azetidone ring in this case is formed early in the synthesis by use of a 2+2 cycloadditon reaction. One component in this condensation consists of the imine (**41-2**) from a glyoxal ester with methyl valinate, with that moiety serving as a chiral auxiliary. Reaction of that with the hypothetical ketene (**41-1**) from carbobenzyloxy glycine and *iso*-butyl chloroformate leads to the azetidone (**41-3**), largely as a single chiral diastereomer. Treatment of the product with sodium carbonate then removes both ester groupings to afford (**41-4**). The free hydroxyl is converted to the carbamate (**41-5**). The valine group on nitrogen is then converted to its iminium salt by anodic oxidation; hydrolysis with potassium carbonate cleaves that function to lead to the secondary amide (**41-6**). That intermediate is then converted to its sulfonic acid derivative with sulfur trioxide, and that hydrogenolyzed to give the primary amine (**41-7**). The amide side chain for this compound also derives from cephalosporin chemistry. In much the same manner as above, amide formation between (**41-8**) and the primary amine (**41-7**) followed by cleavage of the protecting group affords **carumonam** (**41-9**) [44].
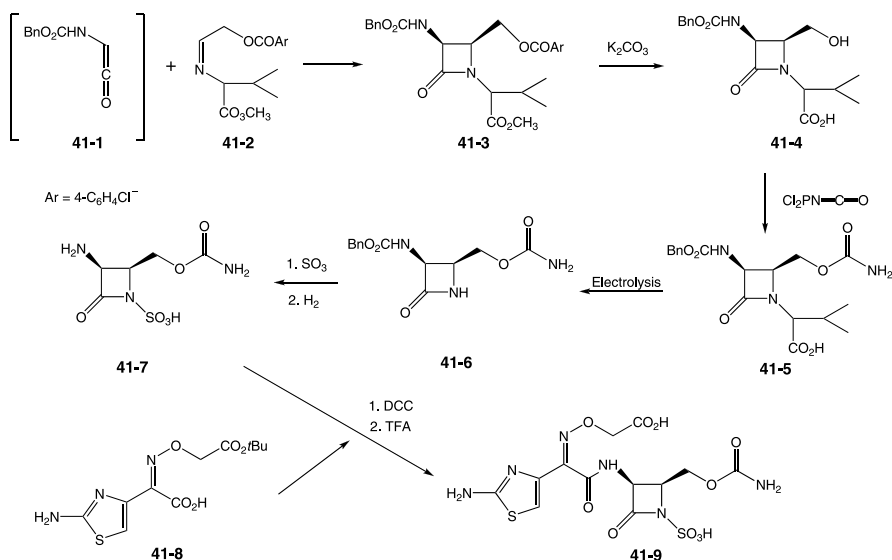
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HETEROCYCLES FUSED TO OTHER
HETEROCYCLIC RINGS

A sizeable number of endogenous compounds that play a key role in the regulation of various life processes in fact consist of fused heterocycles. Two familiar examples include purines, which not only form part of DNA and RNA but also provide the backbone for NADP involved in metabolic electron transport, as well as the pteridines, which are involved in the folic acid cycles. This circumstance combined with the enormous structural diversity available among fused heterocycles has led to their being intensively examined as a source for drugs. A sizeable number of those agents have shown sufficient biological activity to lead to their investigation in clinical trials.

15.1. TWO FUSED FIVE-MEMBERED RINGS

A pyrrolopyrroline carboxylic acid NSAID once again illustrates the structural tolerance in this therapeutic area. The synthesis of this agent starts with Friedel–Crafts acylation of 2-thiomethylpyrrole (**1-2**) with anisoyl chloride (**1-1**) to afford the ketone (**1-3**). The sulfide is then converted to a better leaving group by oxidation to a sulfone (**1-4**) by treatment with peracid. The remaining carbons required for the fused ring are added by means of spirocyclopropyl substituted Meldrum's acid (**1-5**). Reaction of the anion from the pyrrole leads to a ring opening of the cyclopropane ring to give (**1-6**) and, in effect, the addition of a four-carbon chain on nitrogen. Methanolysis of the product leads to an exchange of the acetonide with the alcohol

and thus the formation of the methyl ester (**1-7**). The anion obtained by treatment of the malonate with a base then undergoes internal displacement of the methylsulfone with the consequent formation of the fused pyrroline ring (**1-6**). The ester groups (**1-8**) are then saponified; the resulting malonic acid (**1-9**) decarboxylates on warming to afford **anilorac** (**1-10**) [1].
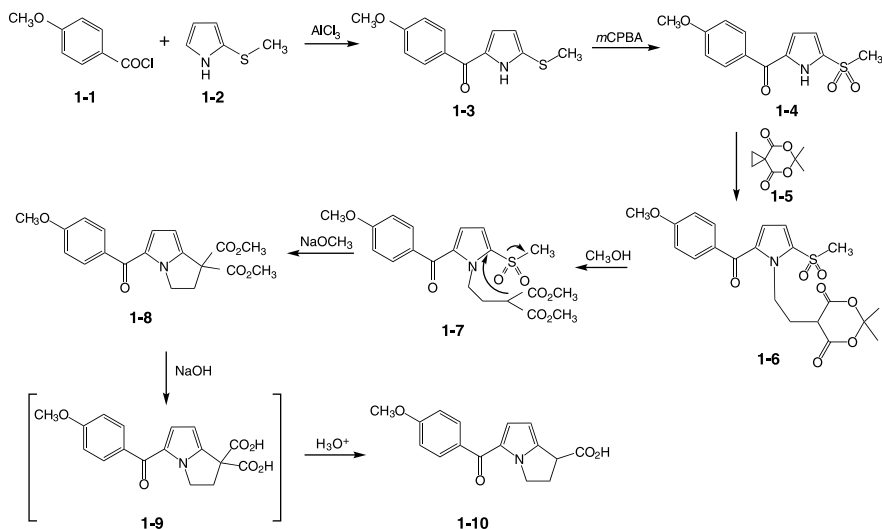
A perhydrofuranopyrrolidine is described as an analgesic that acts by some undefined nonopioid mechanism. Catalytic hydrogenation of the furan ring in diol (**2-1**) leads to the tetrahydro derivative (**2-2**). The method of reduction as well as the subsequent formation of a fused bicyclic product suggest that the hydroxymethyl groups in the product are in the *cis* configuration. The hydroxyl groups are then activated toward displacement by conversion to their *p*-toluenesuflonate esters to give (**2-3**). Reaction of that product with benzylamine then leads to the cyclic *bis*-alkylation
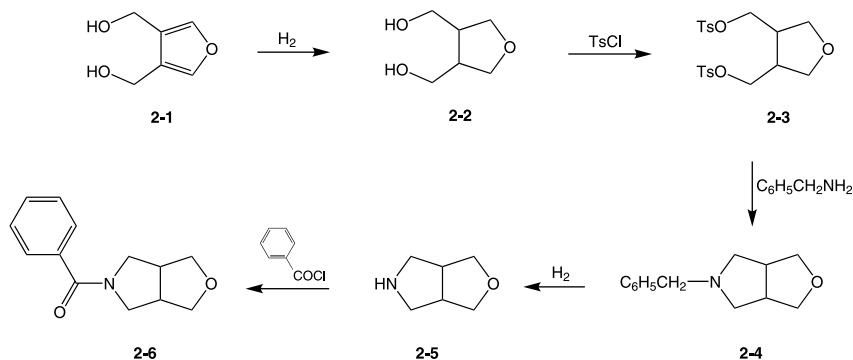
product, (**2-4**) and thus the formation of the pyrrrolidine ring. The benzyl protecting group in the product (**2-4**) is then removed by hydrogenolysis over palladium to give the free secondary amine (**2-5**). Acylation of that group with benzoyl chloride then affords **octazamide** (**2-6**) [2].

The imidazothiazole **tetramisole** (**3-6**) was originally developed as an antihelminstic agent. The levorotatory isomer **levamisole** (**4-3**) was found to be twice as potent as the racemate, though both have been used as veterinary antinematodal drugs. Reaction of 2-aminothiazoline (**3-2**) with phencyl bromide (**3-1**) interestingly occurs on ring nitrogen to afford (**3-3**). The exocyclic imine is then acylated by means of acetic anhydride to afford (**3-4**). Reduction of the ketone with sodium borohydride leads to the benzylic alcohol (**3-5**). Treatment of this intermediate with thionyl chloride leads to a ring closure to (**3-6**) with a simultaneous loss of the acetyl group. There is thus obtained **tetramisole** (**3-6**) [3].
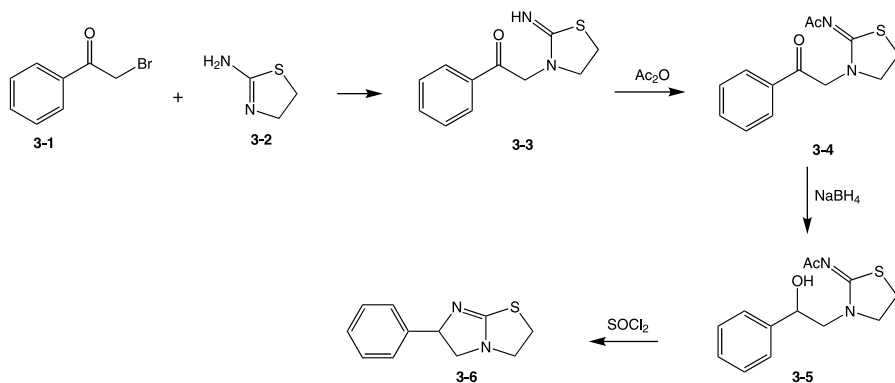
Subsequent investigation revealed that these compounds also have pronounced activity as modulators of the immune system in humans; as a result, **levamisole** now forms part of a multidrug protocol for treating colon cancer. That enantiomer can be prepared stereospecifically by starting with resolved diamine (**4-1**) of known absolute configuration. Reaction with carbon disulfide leads to the mercaptoimidazoline (**4-2**). The remaining ring is then closed by treatment of that product with 1,2-dibromoethane. The absolute configuration of **levamisole** (**4-3**) follows from that of the starting diamine and the fact that none of the transformations involve the chiral center [4].
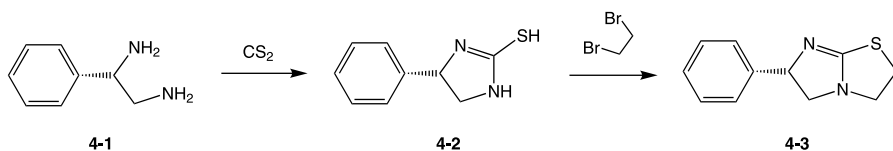
A related scheme starts with the conversion of the exocyclic amino group in 2-methylaminoimidazoline to a good leaving group by conversion to its nitramine derivative (**5-2**). Reaction of that intermediate with phenylethanolamine (**5-1**) leads to the displacement of the nitramine by the primary amine on the reagent and the formation of the substitution product (**5-3**). This is then cyclized with concentrated sulfuric acid to give an imidazoimidazole, probably via the benzylic carbocation. There is thus obtained **imafen** (**5-4**) [5], a compound described as an antidepressant.
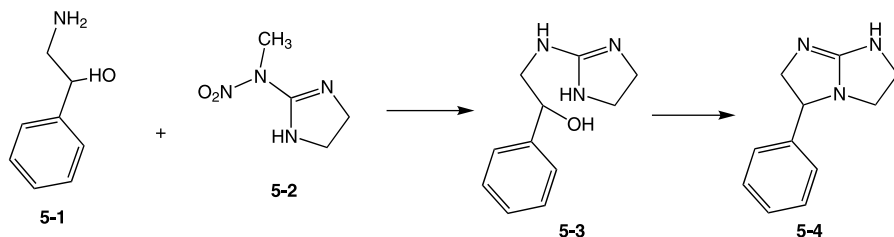
15.2. FIVE-MEMBERED HETEROCYCLES FUSED TO SIX-MEMBERED RINGS

15.2.1. Compounds Containing Two Heteroatoms

The majority of available antihypertensive drugs fall into well-recognized structural and thus pharmacological classes; the furanopyridine **cicletanine** (**6-5**) comprises a compound that reduces blood pressure by decreasing peripheral resistance by a nitric oxide-mediated effect on vascular endothelium. The synthesis of that compound starts with the addition of *para*-chlorophenylmagnesium bromide to the complex pyridine carboxaldehyde (**6-1**). Treatment of the product (**6-3**) with a strong acid proceeds initially to hydrolysis of the acetonide protecting group to afford the transient triol (**6-4**). The benzhydryl carbinol then probably goes to the corresponding carbocation. Capture of the adjacent hydroxyl the forms the dihydrofuran ring and thus **cicletanine** (**6-5**) [6].
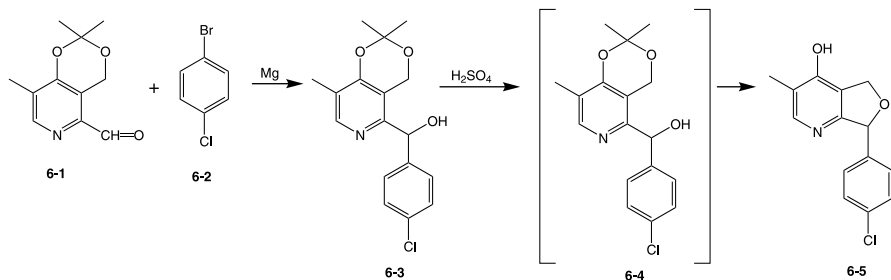
The modification of the Polonovski reaction, which involves a reaction of a pyridine *N*-oxide with phosphorus oxychloride, has been used extensively for the introduction of chlorine at the 2 position. A modification of that reaction allows the introduction of a nitrile group. Thus reaction of the *N*-oxide (**7-2**) from the oxidation of the 2-arylpyridine (**7-1**) with potassium cyanide in the presence of dimethyl sulfate leads to cyanopyridine (**7-3**). The classic Polonovski reaction involves the intermediacy of an *O*-acetate, a role served by an *O*-phosphoryl species in the chlorination; the case at hand can be rationalized by invoking an *O*-sulfated intermediate. The nitrile is then reduced to the primary amine and this converted to the formamide (**7-4**) by exchange with methyl formate. Reaction of that product with phosphorus oxychloride probably proceeds initially to the imino chloride; that cyclizes onto the pyridine ring to give the imidazopyridine (**7-5**). The pyridine ring is then reduced by catalytic hydrogenation to give the intermediate (**7-6**). The carbethoxy group on the pendant benzene ring is converted to its amide by sequential saponification, conversion to the acid chloride, and reaction with ammonia (**7-9**). Treatment of that with phosphorus oxychloride leads to dehydration to a nitrile [7]. This product, **fadrazole** (**7-10**), is one of a series of steroid aromatase inhibitors that share a cyano goup (see **letrozole** et al. Chapter 8).
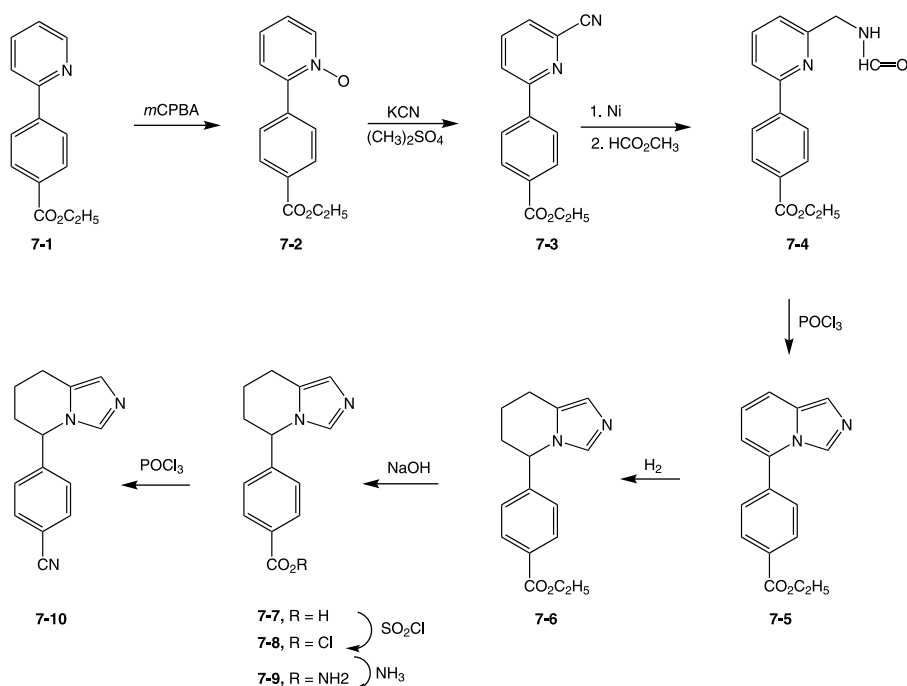
A fully unsaturated imidazopyridine acts as a platelet-aggregation inhibitor. The presence of the fatty acid side chain suggests a possible interaction with arachidonic

acid cascade products. Construction of the fused heterocyclic system parallels that described above. The cyanopicoline (**8-1**) is thus reduced to the amine (**8-2**) and this is converted to formamide (**8-3**). Cyclization with the ubiquitous phosphorus oxychloride gives the key intermediate (**8-4**). Reaction of that compound with butyl lithium abstracts a proton on the methyl group to afford the corresponding carbanion; treatment with the diethyl orthoester from 5-bromopentanoic acid gives the corresponding alkylated product. Hydrolysis of the orthoester group gives the carboxylic acid and thus **pirmagrel** (**8-5**) [8].
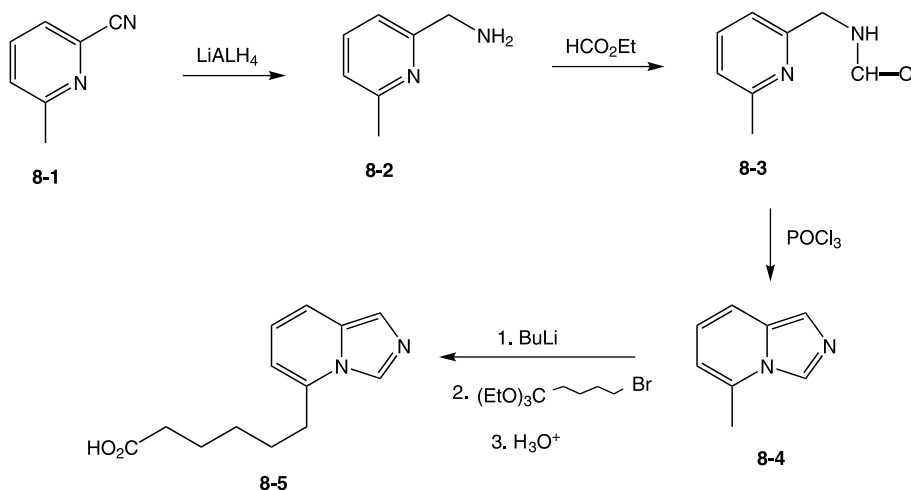
Condensation of a 2-aminopyridine with an α-haloketone provides an alternative method for building the imidazopyiridine. For example, reaction of 2-aminopicoline (**9-1**) with *para*-methylphenacyl bromide (**9-2**) leads directly to the imidazopyridine (**9-4**). The overall transformation can be rationalized by assuming an initial alkylation on ring nitrogen (**9-3**); imine formation followed by bond reorganization then forms
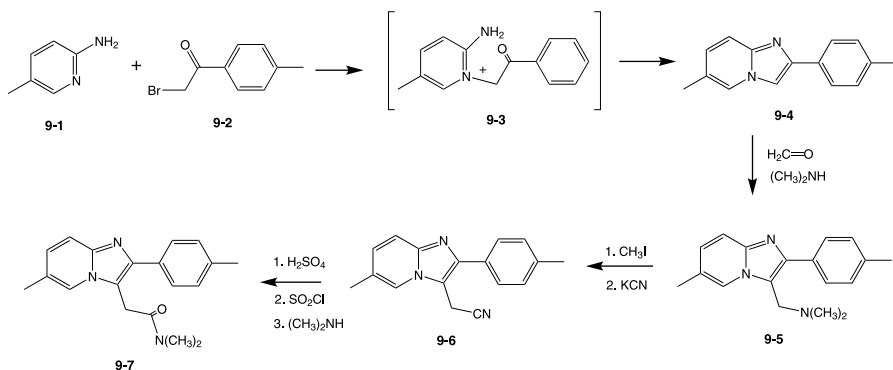
the imidazole ring. Treatment of the product (**9-4**) with formalin and dimethylamine leads to the Mannich base (**9-5**). The dimethylamino group is then activated toward displacement by conversion to the quaternary salt by alkylation with methyl iodide. Reaction with potassium cyanide leads to the acetonitrile (**9-6**). The nitrile is then hydrolyzed to the corresponding amide with acid [9]. This product, **zolpidem** (**9-7**), is a sleep aid agent better known as Ambien®. This compound interestingly interacts with the same receptor as the structurally quite distinct benzodiazepines.

The first published scheme for the preparation of the platelet-aggregation inhibitor ticlopidine describes the alkylation of the thienopyridine (**10-1**) with 2,α-dichoro-toluene (**10-2**) to give the ternary salt (**10-3**). Reaction of that product with sodium borohydride selectively reduces the charged ring to give **ticlopidine** (**10-4**) [10].
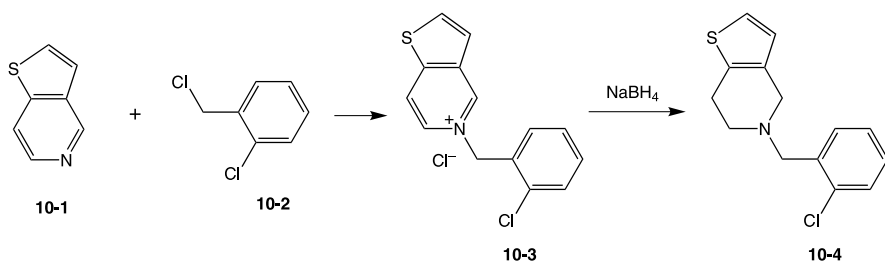
An alternate method for building the partly saturated fused heterocyclic system for **ticlopidine** (**10-4**) starts by formation of the mesylate (**11-2**) from cyanopyridone (**11-1**) by treatment with methanesulfonyl chloride. The reaction of that with butyl thioglycolate can be envisaged as involving, first, the addition of the thiol group to
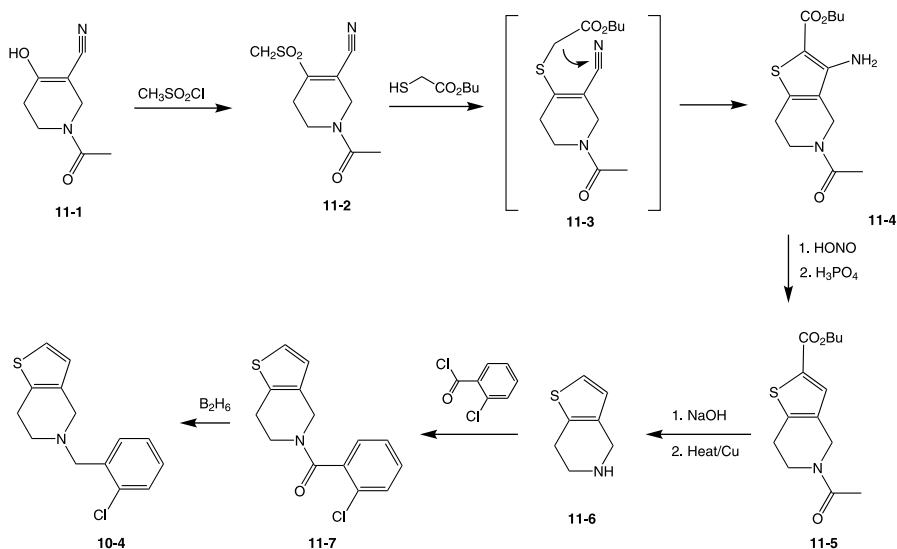
the nitrile to give the iminothioether (**11-3**); displacement of the methanesulfonyl group by sulfur followed by internal aldol condensation will lead to the observed product (**11-4**). The amino group is then converted to its diazonium salt with nitrous acid and this reduced by reaction with hypophosphinic acid (**11-5**). Treatment with an aqueous base then hydrolyzes both the ester and the acetyl group of nitrogen. The resulting acid is then decarboxylated by heating in the presence of copper powder to give the piperidinothiophene (**11-6**) [11]. Acylation of that product (**11-7**) with *ortho*-benzoyl chloride followed by reduction of the amide will afford **ticlopidine** (**10-4**).

Adding a carboxylic acid to ticlopidine will arguably enhance the biopharmaceutical propers of the parent molecule. The presence of a chiral center in that drug invokes the need for the use of a resolved starting material. The synthesis of that compound, **clopidogrel** (**12-4**), involves yet another approach to the ring system. Thus, alkylation of S-(+)-2-chlorophenylglycine methyl ester (**12-2**) with 2-chloro-ethylthiophene (**12-1**) leads to the secondary amine (**12-3**). Treatment of that product under Clark–Eshweiler conditions (formic acid and formaldehyde) likely leads initially to the formation of the corresponding carbinolamine. This intermediate or its iminium dehydration product then attacks the thiophene to close the fused ring, affording clopidogrel, (**12-4**) [12].
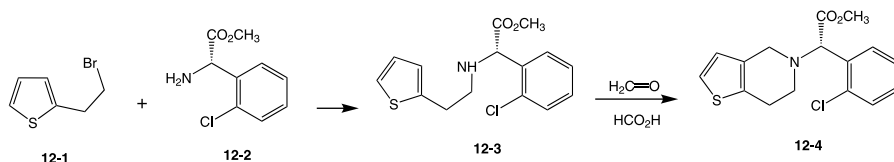
The synthesis of the aggregation inhibitor **prasugrel** (**1-9**) illustrates yet another approach to the fused thienopioperidine. Alkylation of the enolate from treatment of N-(4-chlorobenzyl)piperidine (**13-1**) with sodium hydride with ethyl chloroacetate affords the ketoester (**13-2**). Reaction of that product with hydrogen sulfide leads to the formation of the thiolactone (**13-3**) [13]. This transform can be rationalized by assuming the initial conversion of the ketone to a thioenol; that then attacks the ester to close the ring. Reaction of the product would then form the corresponding enol acetate (**13-4**). In a convergent sequence, the Grignard reagent from the benzyl bromide (**13-5**) is added to cyanocyclopropane (**13-6**). This affords the ketone
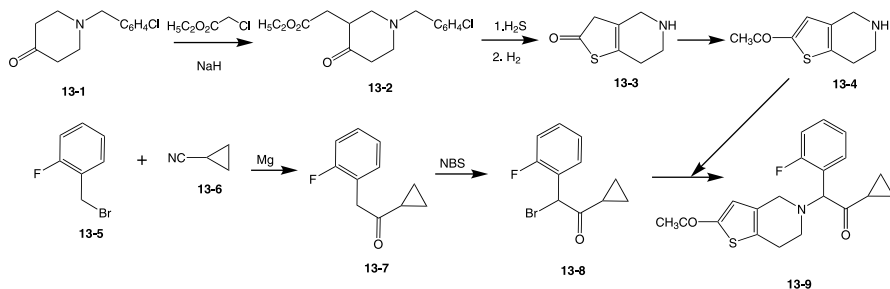
(**13-7**) after hydrolysis. Treatment of this intermediate with *N*-bromosuccinimide leads to the formation of the brominated derivative (**13-8**). Reaction of this last with the thienopiperidine (**13-4**) leads to the displacement of bromine and the formation of the alkylation product. There is thus obtained prasugrel (**13-9**) [14].

Prompted by the involvement of gamma-aminobutyric acid in a host of CNS processes, a close analogue of muscimol, the GABA agonist from the *amanita* mushroom has been investigated as a sleep aid. The drug reduces insomnia and improves the quality of sleep. The synthesis of this compound begins by forming the acetal from (**14-1**) by reaction of the compound with ethylene glycol (**14-2**). Reaction of this intermediate with hydroxylamine replaced by the ethoxy group in the ester affords the hydroxamic acid (**14-3**). Treatment of that intermediate with acid leads first to the hydrolysis of the ketal; reaction of the terminal hydroxyl on the hydroxylamine group with the ketone leads to the closure of the isoxazole ring (**14-4**). Hydrolysis under more strenuous conditions frees the piperidine nitrogen to afford **gaboxadrol** (**14-5**) [15].
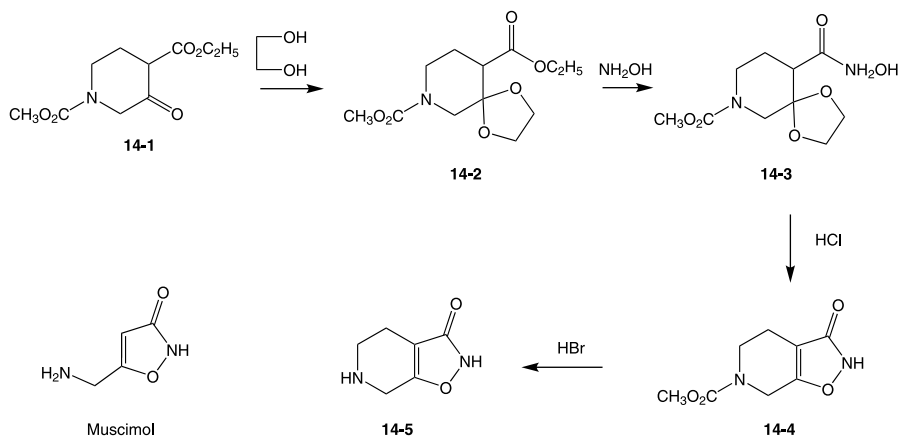
The sulfonamido group constitutes an important moiety in the classical carbonic anhydrase diuretic agents such as **acetazolamide** (see Chapter 8). The observed reduction in ocular pressure by such agents in glaucoma patients led to the development of more specific agents based on the thiophenothiopyran nucleus. The enantioselective synthesis of this agent starts with reaction of lithiated thiophene (**15-2**) with sulfur to give the salt (**15-3**) of the corresponding thiol. This is reacted *in situ* with 3-bromopropionic acid to afford the alkylation product (**15-4**). Treatment with trifluoroacetic anhydride leads to a Friedel–Crafts-type cyclization of the byclic compound (**15-5**). Sodium periodate acid selectively oxidizes sulfur in the dihydrothiopyranone ring to give the sulfone (**15-6**). Reduction of the carbonyl group with a chiral oxazaborolidine hydride then affords the corresponding alcohol (**15-7**) in high enantiomeric excess, though in the opposite configuration from that desired in the final product. The alcohol is then converted to the tosylate (**15-8**); displacement with isobutylamine gives the amine derivative (**15-9**) of the opposite configuration. The all-important sulfonamide group is then introduced by first reacting the compound

with chlorosulfonic acid. Treatment of the thus-obtained sulfonyl chloride (**15-10**) with ammonia gives the ocular carbonic anhydrase inhibitor **sezolamide** (**15-11**) [16].
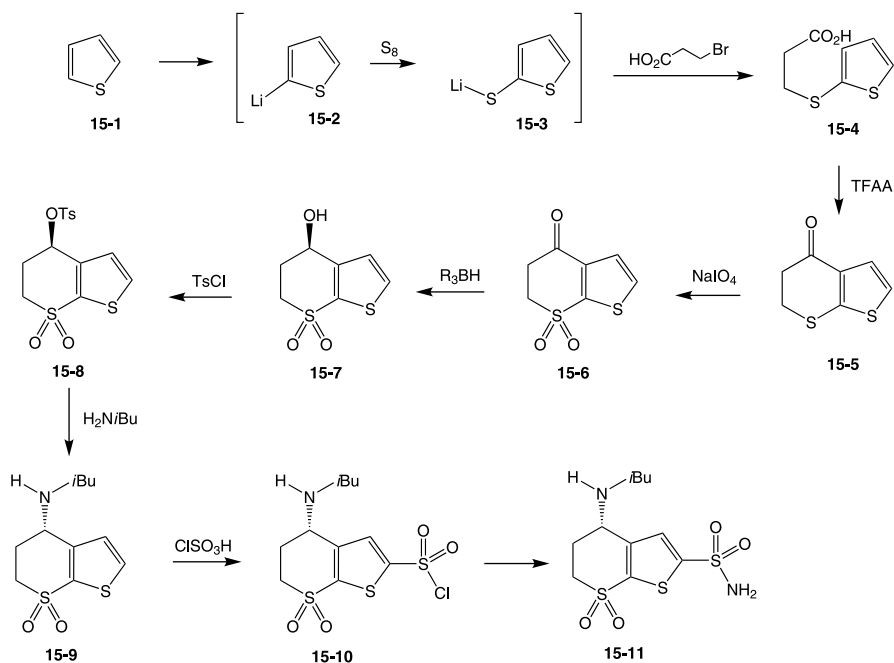
15.2.2. Compounds Containing Three Heteroatoms

The reaction used for the construction of the starting material for a pyrrolo-pyridine involves the standard pyrimidine chemistry discussed in Chapter 9. Thus condensation of the substituted cyanoacetate (**16-1**) with acetamidine leads to the
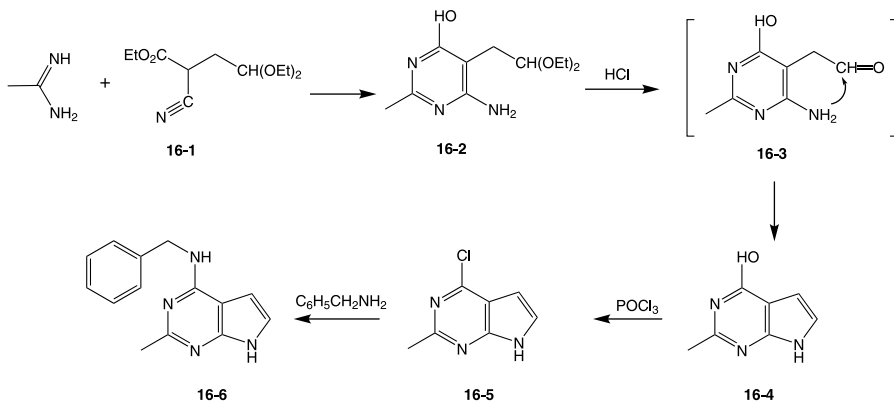
aminopyrimidinol (**16-2**). Treatment of that intermediate with acid leads to the hydrolysis of the acetal and the formation of the transient free aldehyde (**16-3**). This then undergoes internal imine formation to afford the fused heterocycle (**16-4**). The enol is converted to the chloride (**16-5**) in the usual way by reaction with phosphorus oxychloride. Displacement of chlorine with benzylamine leads to the muscle relaxant **rolodine** (**16-6**) [17].

The utility of modified pyrimidines for the treatment of viral diseases and cancer, in Chapter 9, applies as well to purine heterocycles. **Dezaguanine** (**17-8**), in which one of the pyrimidine nitrogens found in guanine is replaced by carbon, has, for example, been tested as a cancer chemotherapeutic agent. The aminoketone (**17-1**) is available from acetone dicarboxylic ester by successive nitrosation followed by reduction of the nitroso derivative. Reaction of that product with potassium iso-thiocyanate can be envisioned as leading initially to the thiourea (**17-2**). This cyclizes spontaneously to the imidazothione (**17-3**) under reaction conditions. Treatment of that product with liquid ammonia leads to the preferential exchange of the uncon-jugated ester group to give the amide (**17-4**); the greater reactivity can be attributed to the higher electron density at that carbonyl group. This is then desulfurized by reaction with Raney nickel to give the imidazole (**17-5**). Treatment of that inter-mediate with phosphorus oxychloride then serves to dehydrate the amide group to a nitrile to give (**17-6**). The remaining ester group is converted to the amide (**17-7**) by reaction with ammonia under more strenuous conditions. That function cyclizes onto the nitrile when treated with sodium carbonate to afford **dezaguanine** (**17-8**) [18].
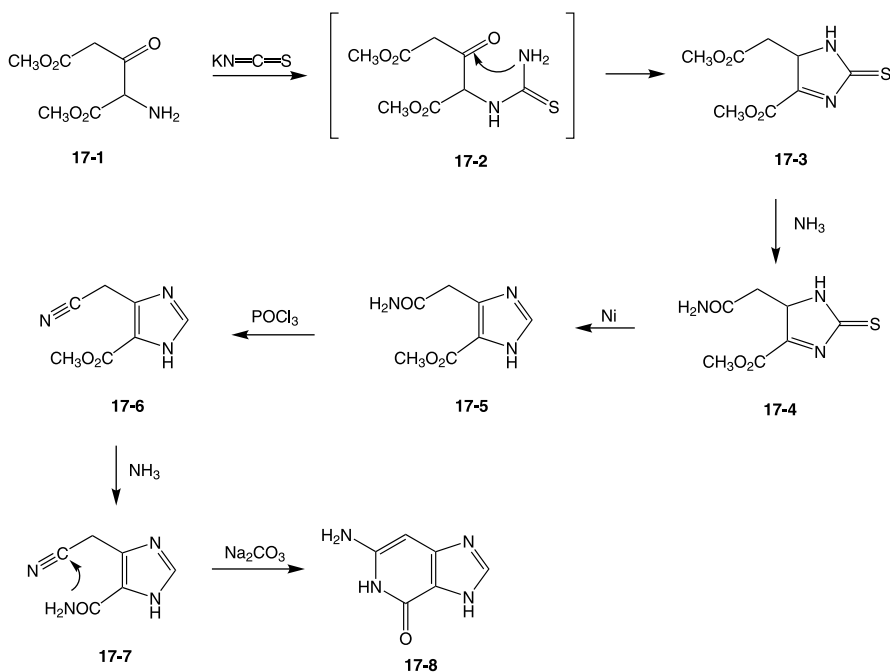
The ring system that provides the core for the cardiotonic agent **isomazole** (**18-7**) may be viewed as a pyridine analogue of a benzimidazole; the chemistry used to form that ring system is in fact quite analogous to that discussed in Chapter 10. The preparation of the requisite benzoic acid involves the conversion of a phenol to a thiophenol using the thiocarbamate interchange reaction. Thus the phenol (**18-1**) is acylated with dimethylaminothioformyl chloride to give the carbamate (**18-2**). This product undergoes O to S aryl migration on heating to give the isomeric carbamate (**18-3**). Treatment with an aqueous base then removes the carbamate and at the same time serves to saponify the ester. Reaction of the product with methyl iodide in the presence of a base alkylates both the thiophenol and the carboxyl group; a second saponification restores the free acid to give (**18-4**). This is then condensed with the diaminopyridine analogue (**18-5**) of phenylene diamine to yield the substituted imidazopyridine (**18-6**). Oxidation of the thioether in that compound with peracid under controlled conditions gives the sulfone and thus **isomazole** (**18-7**) [19].
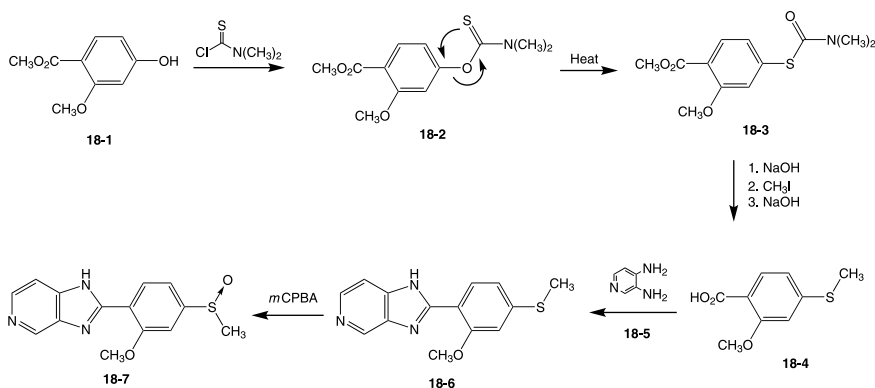
In a sequence reminiscent of the scheme used to build the heterocyclic ring in quinolones (Chapter 11), condensation of aminopyrrazole (**19-2**) with ethyl
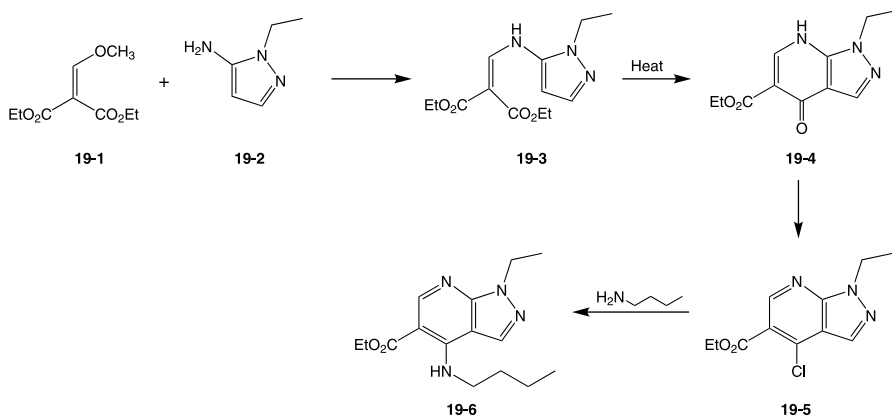
methoxymethylene malonate (**19-1**) proceeds to give the corresponding imine (**19-3**), probably by an addition-elimination sequence. One of the carbethoxy groups cyclizes onto the heterocyclic ring when that intermediate is heated in diphenyl ether to give the fused pyridone (**19-4**), shown as its keto tautome. Reaction of that intermediate with phosphorus oxychloride leads to the enol chloride (**19-5**). That reactive group is then displaced by butylamine to give **cartazolate** (**19-6**) [20], a compound described as an antidepressant.

A rather complex seeming triazolopiperidine is prepared by a surprisingly simple two-component condensation. Reaction of the hydrazide (**20-2**) with the iminoether (**20-1**) from 2-piperidone can be rationalized by assuming the initial formation of an intermediate such as (**20-3**) by an addition–elimination sequence. The second step involves an attack on the carbonyl group by the now quite basic ring amidine nitrogen. The observed product, **dapiprazole** (**20-4**) [21], displays α-adrenergic blocking as well as antipsychotic activity.
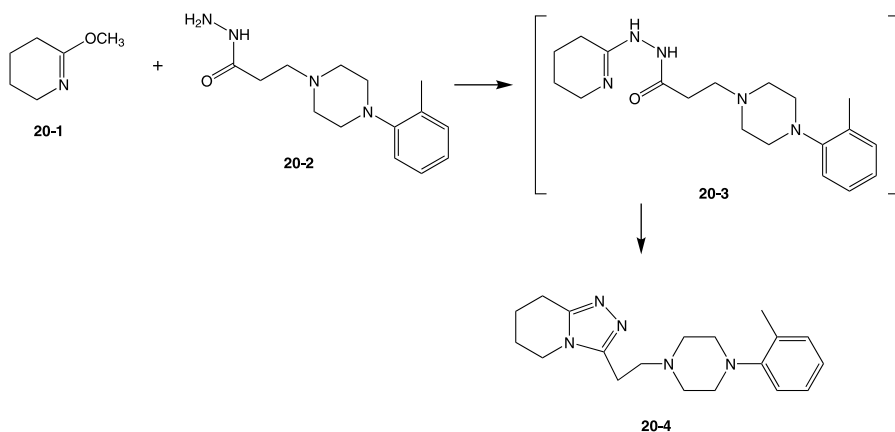
Benzodiazepines typically display other activities in addition to the anxiolytic effects. These ancillary activities sometimes dominate, as in the case of benzodiazepine soporific agents. The identification of receptors for this class of drugs has led to a search for compounds that will interact with subsets that promise more specific agents. A pair of related pyrrazolopyrimidines bind preferentially to receptors associated with sleep. The preparation of the first of these starts with the reaction of the acetophenone (**21-1**) with dimethylformamide acetal to give the enamide (**21-2**). The anion from the reaction of anilide nitrogen with sodium hydride is then alkylated with ethyl iodide (**21-3**). Reaction of this last intermediate with pyrrazole (**21-4**) can be rationalized by assuming formation of the product (**21-5**) from the displacement of the enamide nitrogen by the amine on the pyrrazole. Cyclization then leads to the pyrrazole pyrimidine ring system and thus the formation of the sleep inducing agent **zaleplon** (**21-6**) [22].
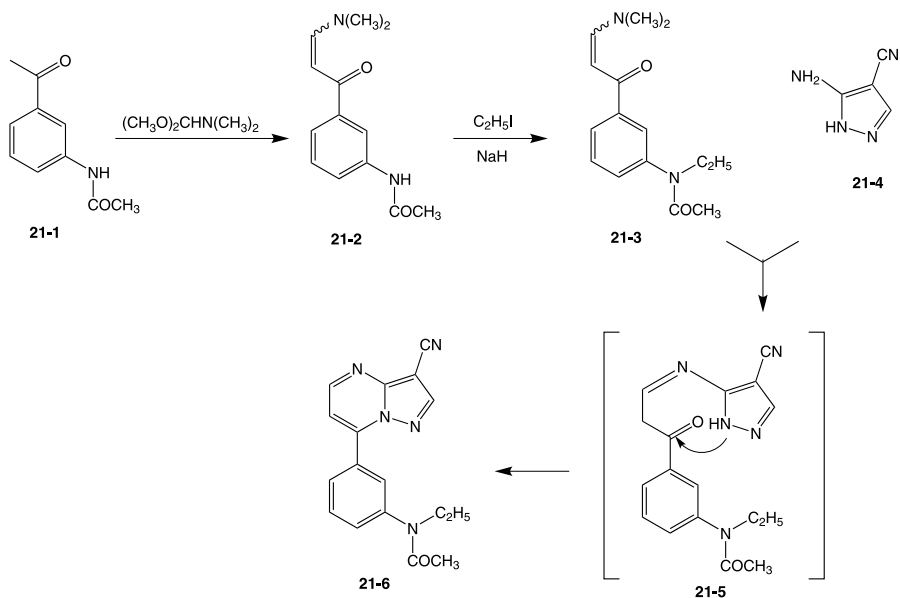
An analogous scheme is used to prepare a more highly nitrogenated compound. Thus, reaction of acylpyridine (**22-1**) with dimethylformamide acetal gives enamide (**22-2**). Condensation of that with the somewhat more complex pyrazole (**22-3**) leads to the soporific agent **ocinaplon** (**22-4**) [23].
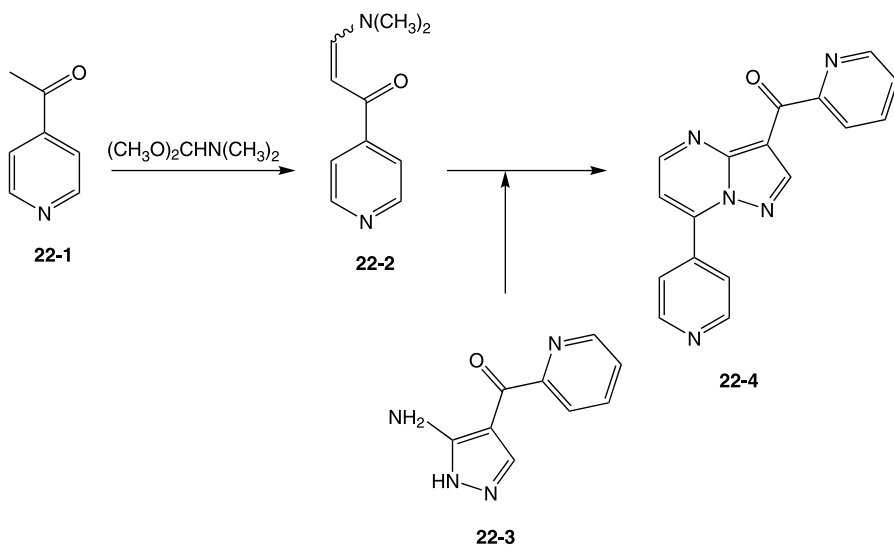
   The synthesis of yet another example begins with the allylation of the enamide (**21-2**) with methyl iodide. Reaction of this intermediate (**23-1**) as above with the aminopyrrazole (**23-2**) leads to the formation of the fused pyrimidinopyrrazole (**23-3**). This last productis is next acylated with thiazole-carboxillic acid (**23-4**) in the presence of aluminum chloride. There is thus obtained the sleep inducing agent **indiplon** (**23-5**) [24].
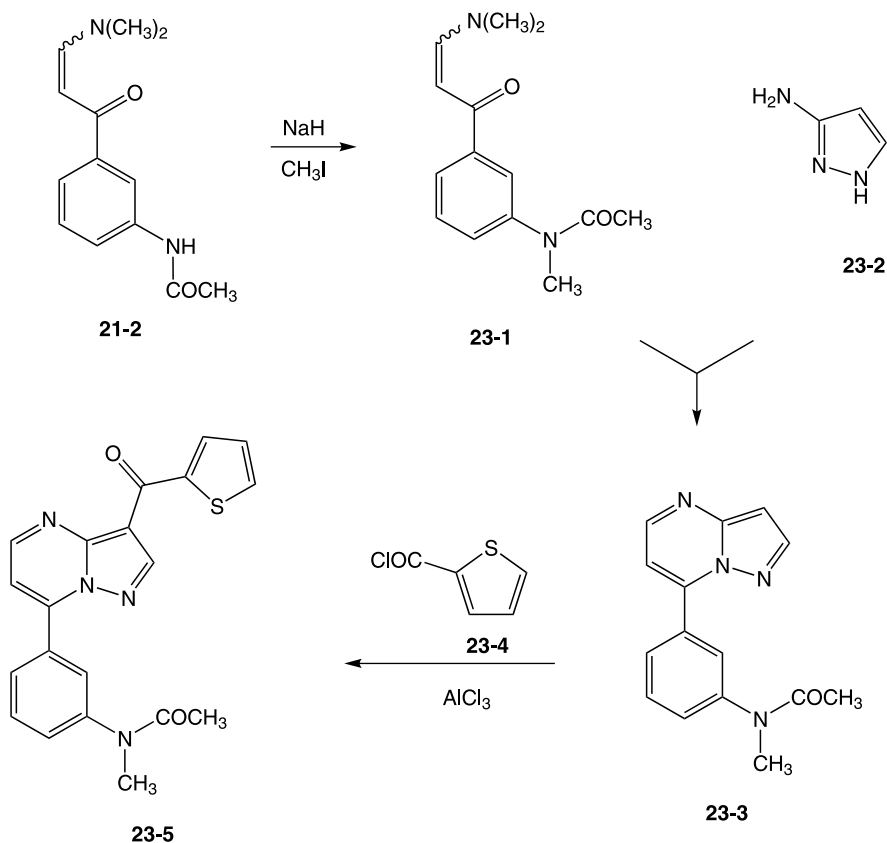
   Purines play a very central role in cell replication, forming not only an important part of the genetic material but also the molecules that guide the process. This has led to a large amount of research on purines as potential antineoplastic agents. The antineoplastic agent **peledesine** (**24-11**) can be viewed as a deaza adenine in which the sugar is replaced by a pyridylmethyl moiety. The rather lengthy synthesis involves building the two rings of the purine in a stepwise fashion. Condensation of nicotinaldehyde (**24-2**) with ethylcyanoacetic acid leads to a Knoevnagel-like reaction with a loss of carbon dioxide to afford the acrylonitrile (**24-3**). Treatment with sodium borohydride then reduces the olefin to afford the propionitrile (**24-4**). Reaction of this last intermediate with ethyl formate and sodium hydride leads to the formyl derivative

(**24-5**). The nitrogen required for the future pyrrole ring is introduced by condensation of (**24-5**) with ethyl glycinate. The product from the addition-elimination sequence is then allowed to react with ethyl chloroformate to give the corresponding amide (**24-6**). The ring is then closed by addition of the anion next to the ester in (**24-6**) with the base 1,5-diazabicyclo(4.3.0)nonene (DBN) to the nitrile to yield (**24-7**). The acyl group on ring nitrogen is next removed by means of an aqueous base to give the free amine (**24-8**). Treatment with benzoyl isothiocyanate then gives the addition product, benzoyl thiourea (**24-9**). Sulfur is next activated as a leaving group by conversion to its *S*-methyl ether by means of methyl iodide. The final step can be rationalized by positing an initial replacement of the *S*-methyl ether by ammonia (**24-10**). This group then attacks the ester on the pyrrole, closing the second ring. The benzoyl group on the side chain is ammonolyzed under reaction conditions to afford **peledesine** (**24-11**) [24].
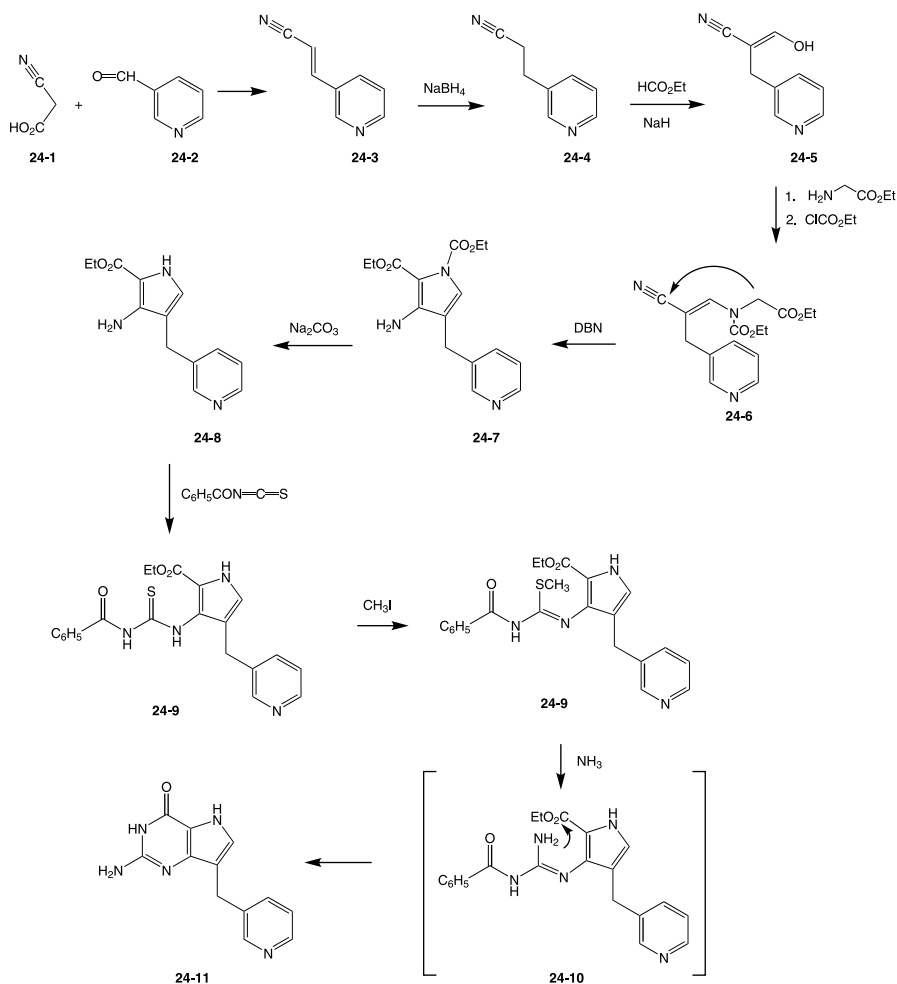
Benzene and thiophene rings can of course often be interchanged in biologically active agents. The very broad structural latitude consistent with NSAID activity is by now a familiar theme as well. Preparation of the fused thiophene counterpart of the NSAID **piroxicam** (Chapter 11) starts with the reaction of thiophene (**25-1**), itself the product of a multistep sequence, with ethyl *N*-methylglycinate to give the sulfonamide (**25-2**). Treatment of that intermediate with a base leads to intramolecular Claisen condensation and thus the formation of the β-ketoester (**25-3**). An amide-ester interchange with 2-aminopyridine (**25-4**) completes the synthesis of **tenoxicam** (**25-5**) [25].
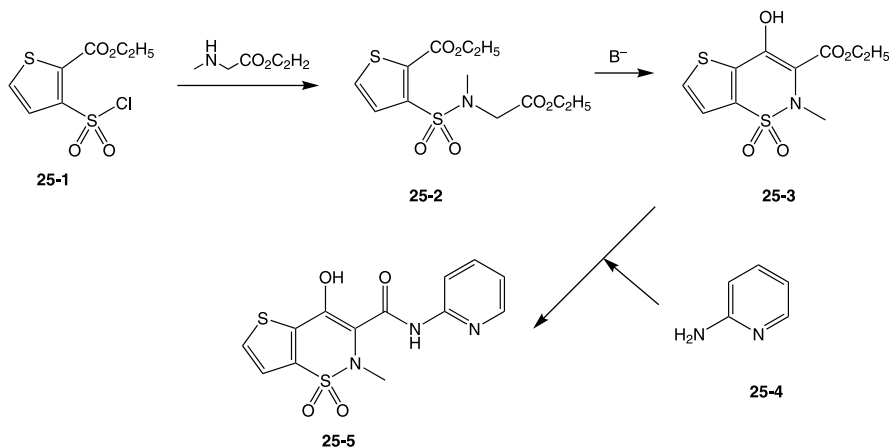
15.2.3. Compounds with Four Heteroatoms

15.2.3.1. Purines

15.2.3.1.1. Phosphodiesterase Inhibitors. The recognition of the biological activity of the simple purines, exemplified by caffeine, predates the formal study of pharmacology by several centuries. Infusions that contain those bases, also called methylxanthines, such as coffee and tea have of course long been used for their CNS stimulant properties. There is also some anecdotal evidence for the bronchodilating activity of caffeine. The use of **theophylline** (**26-7**), which lacks the imidazole *N*-methyl group of caffeine, in the treatment of asthma is, however, of more recent origin and was first used on the basis of empirical observations. It is now recognized that this compound inhibits the hydrolysis of cyclic esters of nucleotides, mainly cyclic adenosine monophosphate, cAMP, and as a result prolongs the relaxant action of that mediator. The first sequence in one of the syntheses of that compound consists of typical pyrimidine chemistry. Thus amide-ester interchange between *N,N'*-dimethyl urea (**26-1**) and ethyl carboxamidoacetate (**26-2**) leads to the acylurea (**26-3**). This cyclizes to the aminopyrimidone (**26-4**) on treatment with a base. A second nitrogen substituent on the ring is introduced by treating that intermediate with nitrous acid to afford the nitroso derivative (**26-5**). The newly introduced function is then readily reduced to yield diamine (**26-6**) under any of several conditions, such as, for example, reaction with zinc in mineral acid. The fused imidazole ring is

then closed by condensing the diamine with formic acid, or some formic acid equivalent such as ethyl orthoformate, to give **theophylline (26-7)** [26].
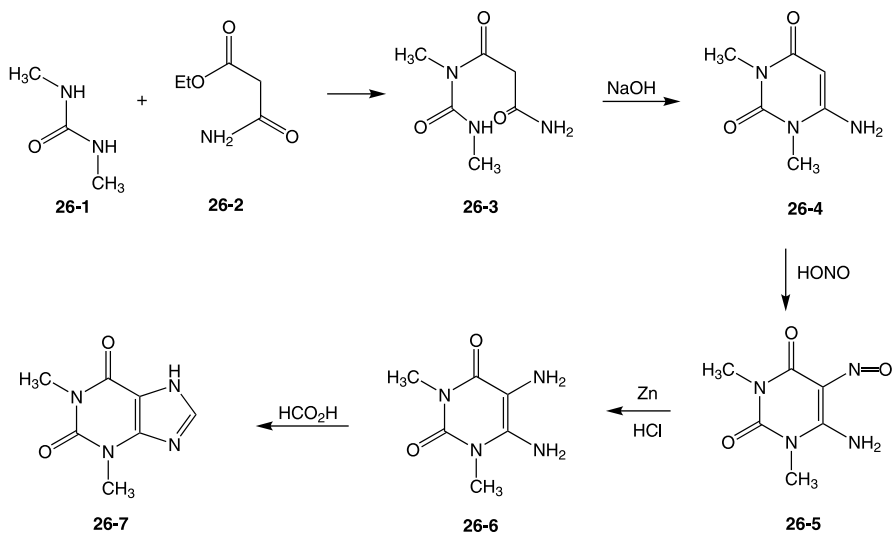
Though very effective, **theophylline** has a number of significant drawbacks as a drug, not the least of which is its very narrow therapeutic window: Minimally effective blood levels are in the range of $10\,\mu g/mL$ while toxic signs are seen as at twice that concentration. One approach to improving the biological properties of drugs involves increasing the lipophilicity and thus presumably the bioavailability. The synthesis of a more lipophillic analogue of theophylline substitutes the isopentyl substituted urea (**27-1**) in the scheme outlined above to give the pyrimidinone (**27-2**);
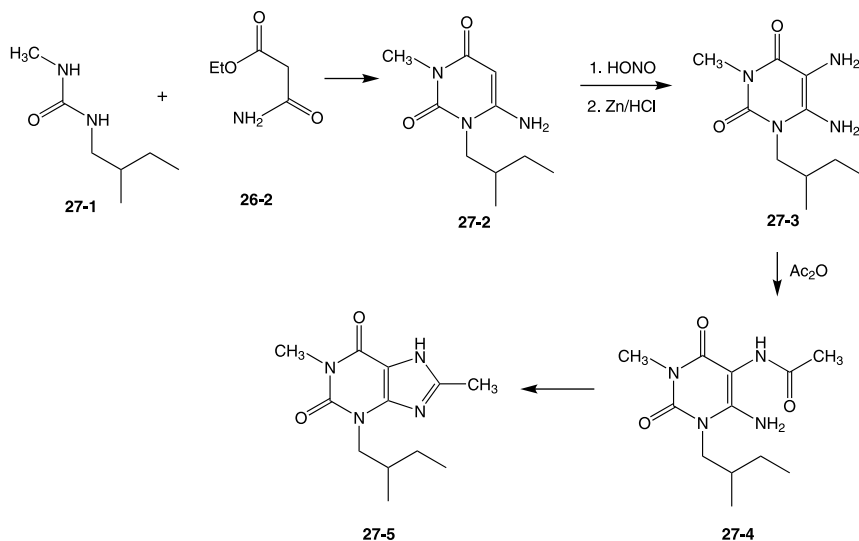
the initial ester interchange at the *N*-methyl nitrogen is probably guided by the less hindered milieu about that center. Sequential nitrosation and reduction of the resulting nitroso compound gives the diamine (**27-3**). The remaining carbon atom is introduced in a stepwise fashion in this case. Thus, reaction with acetic anhydride leads to the amide (**27-4**). This cylcizes to **verofylline** (**27-5**) on reaction with a base [27].

Acylation of the theophylline diamine intermediate (**26-6**) with phenylacetyl chloride affords the corresponding amide (**28-2**). Base catalyzed cyclization then leads to the purine (**28-3**) that now includes a quite lipophilic benzyl group on the fused imidazole ring. The molecule is then provided with a side chain that incorporates basic nitrogen, arguably to improve water solubility. The anion from (**28-3**) is thus first alkylated with bromochloroethane to afford the chloroethyl product (**28-4**). The displacement of chlorine with ethanolamine affords the bronchodilator **bamifylline** (**28-5**) [28].
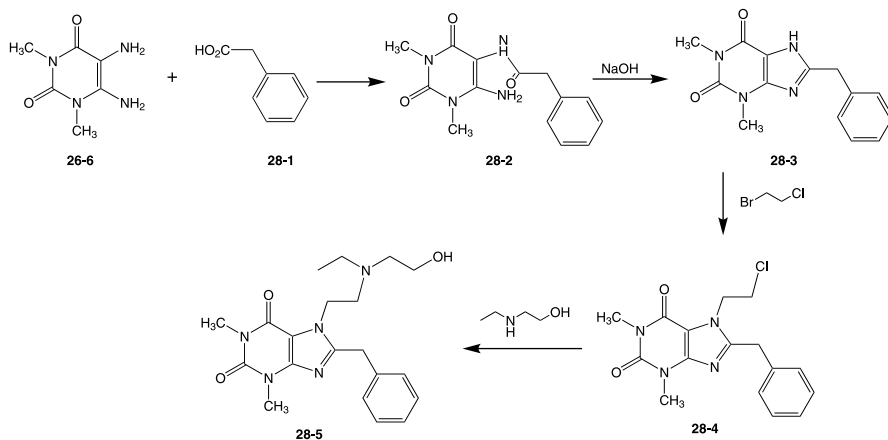
An aliphatic group on the imidazole ring serves much the same fuction as the benzyl group in bamifiline. Condensation of the ketal from 3-oxo-cyclopentane
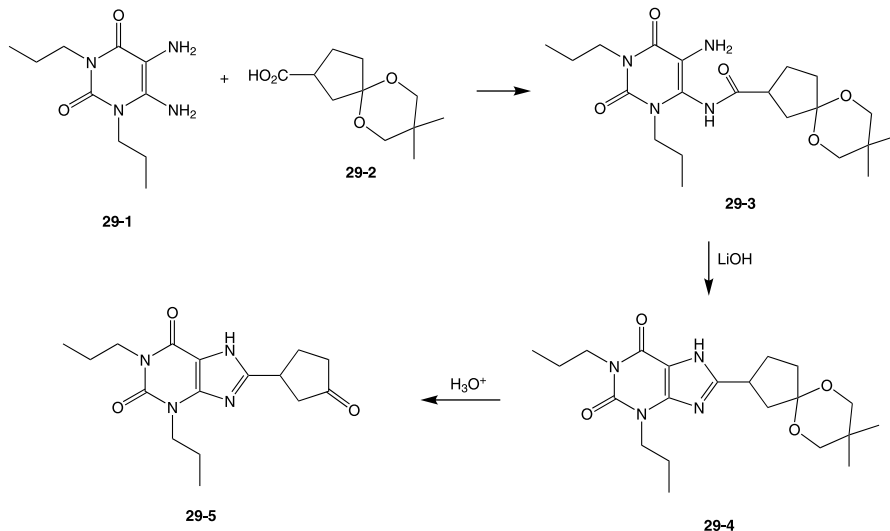
carboxaldehyde (**29-2**) with the *N,N*-bispropyl analogue (**29-1**) proceeds on the more basic nitrogen to afford the amide (**29-3**). This is then cyclized by means of a base. The protecting group is removed by treatment with aqueous acid. There is thus obtained the antiasthma compound **apaxifylline** (**29-5**) [29].

Substituting a fatty side chain on the imide nitrogen in the six-membered ring leads to a compound used mainly as a vasodilator. One preparation for the readily available starting material, theobromine (**30-2**), involves the reaction of the formamido (**30-1**) with dimethyl sulfate in the presence of a base. The first step is thought to consist of methylation on the formamide nitrogen; this cyclizes to theobromine (**30-2**) under reaction conditions. The anion from the only remaining ionizable imide nitrogen is then alkylated with 6-chlorohexan-2-one to give **pentoxyfylline** (**30**) [30].
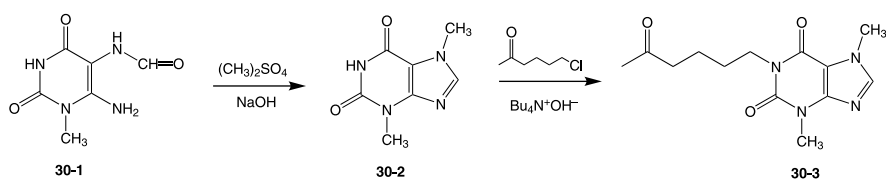
The *R* enantiomer of the pentoxyfylline analogue in which the ketone has been reduced to an alcohol shows enhanced activity as an inhibitor of acetyl CoA over the
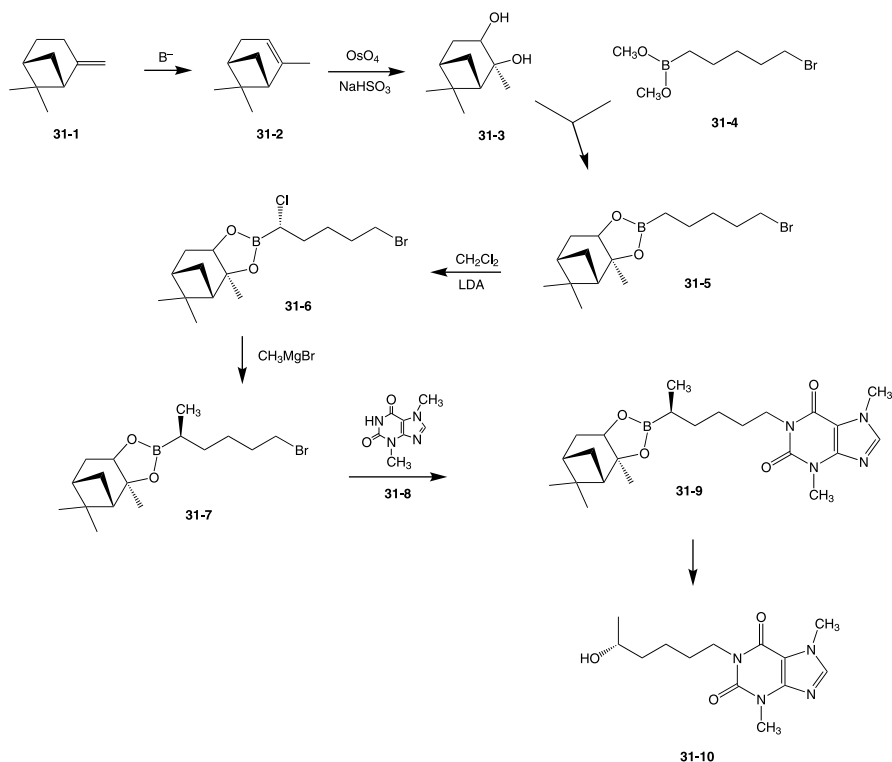
parent drug. The drug may also find use in chemotherapy by protecting healthy cells. The enantioselective synthesis of the side chain depends on the transfer of chirality from β-pinene (**31-1**). Treatment of that terpene with a base moves the usaturation into the ring (**31-2**). That bond is then oxidized to the corresponding diol (**31-3**) by means of osmium tetroxide in the presence of sodium bisulfite. In a convergent scheme, 5-bromopent-1-ene is reacted in turn with boron trichloride and with triethyl silane in methanol to afford the methyl boronate ester (**31-4**). Ester interchange between this product and the glycol in the terpene derived glycol (**31-3**) leads to the cyclic boronate (**31-5**). Reaction of the anion next to boron from (**31-5**) and lithium diisopropyl amide with methylene chloride leads to chloride (**31-6**). This product is obtained as a single enantiomer due to the presence of the adjacent chiral auxiliary. Treatment of (**31-6**) with methylmagnesium bromide results in the displacement of the reactive halogen by the methyl group with an inversion of configuration (**31-7**). This last intermediate is then used to alkylate the purine (**31-8**) in the presence of a base to afford (**32-9**). Treatment with hydrogen peroxide oxidizes the carbon–boron bond, replacing bron by a hydroxyl group. This last step yields the target molecule **lisofylline** (**31-10**) [31] as a single stereoisomer. The other product comprises glycol (**31-3**), which can be recycled.

Replacing the hydrogen atom on the imidazole ring of a purine with some large lipophillic group leads to compounds that are no longer PDE inhibitors but instead act as adenosine receptors antagonists. The first of these, **istradefylline** (**32-5**), selectively blocks A(2A) receptors and in addition inhibits monoamine oxidase B (MAO-B). The neuroprotective action of this agent in animal models for Parkinson's disease has been attributed to this mixed activity. Reaction of the diamine (**32-1**) with the 3,4-dimethoxy cinnamic acid (**32-2**) in the presence of a diimide leads to the formation of a mixture of the amides formed between the acid and one of the two amines on the pyrimidine (only one, (**32-3**), shown). Heating that mixture with sodium hydroxide leads to cyclization to form the xanthine (**32-4**). The free amine on
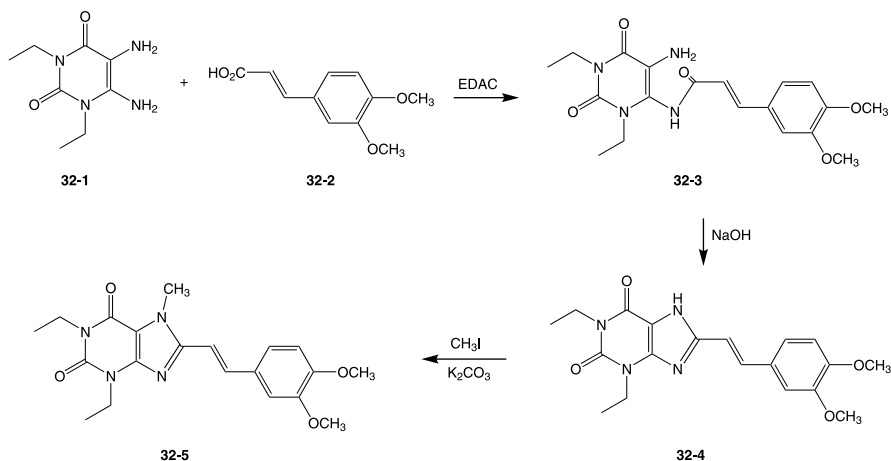
the fused imidazole is then alkylated with methyl iodide in the presence of a base to afford istradefylline (**32-5**) [32].

Substitution by an unusual bridged biyclic moiety also provides a compound that acts as an adenosine A1 receptor antagonist. These ubiquitous receptors, which are involved in regulating oxygen consumption and the flow of blood in cardiac tissue, generally suppress those functions. An antagonist would thus be potentially useful for the treatment of congestive heart failure. The xanthine portion of this molecule is constructed much the same way as in the previous case. Thus, acylation of the diamino pyrimidine (**33-1**) with acryloyl chloride (**33-2**) in this case affords solely the amide from reaction at the more basic amine (**33-3**). Reaction with a base again closes the imidazole ring to give xanthine (**33-4**). Diels-Alder condensation of the vinyl group on this ring with cyclopentadiene proceeds to form the bridged bicylic system (**33-5**). Oxidation of the isolated double bond on that newly formed moiety with metachloroperbenzoic acid then affords the oxirane (**33-6**). There is thus obtained the adenosine antagonist **naxifylline** (**33-6**) [33].
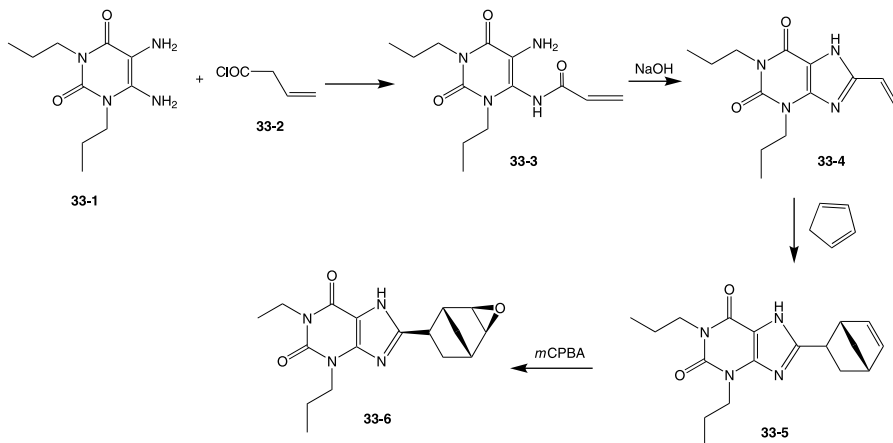
The discovery of subtypes of receptors and enzymes has, over the past several decades, provided the basis for the development of drugs that more specifically address various disease states. Phosphodiesterase, for example, was found to occur in at least five different flavors. A whole new area of drug therapy arose when a compound that preferentially acts against PDE V was taken to the clinic as a potential antihypertensive agent. The adventitious finding that the compound affected erectile function led to a new research target. The activity was traced to unexpectedly high levels of PDE V in the corpus cavernosum, where inhibitors promote relaxation of the muscle that admits blood. The synthesis starts with the reaction of the beta dicarbonyl ester (**34-1**) with hydrazine to yield the pyrrazole (**34-2**) that will form the five-membered ring of the modified xanthine. The free amine is next converted to the N-methyl derivative (**34-3**) by means of dimethyl sulfate. The ester is next saponified with a base (**34-4**). Reaction with nitric acid introduces a nitro group on the only open position on the heterocycle (**34-5**). The carboxylic acid is taken on to the

corresponding amide (**34-7**) by sequential reaction with thionyl chloride and then ammonia. Treatment of that intermediate with stannous chloride serves to reduce the nitro group to a primary amine (**34-8**). Acylation of that product with ethyl salicyl chloride (**34-9**) leads to the *bis*-amide (**34-10**). Treament with a base leads to cyclization the modified xanthine (**34-11**) in one of the classical methods for forming pyrimidone rings. Chlorosulfonic acid then attacks the position *para* to the alakoxy group on the pendant ring (**34-12**). Reaction of the chlorosulfony group with *N*-methylpiperazine (**34-13**) leads to the sulfamide (**34-14**) and thus the PDE V inhibitor **sildefanil** [34].
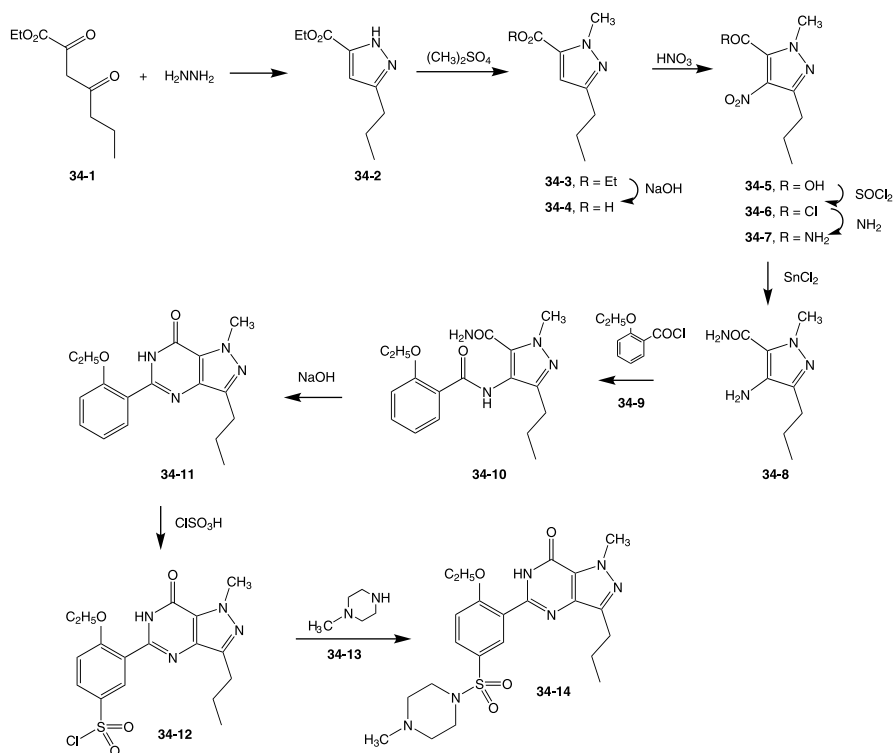
Much the same activity is retained when the nitrogen atoms in the heterocyclic nucleus are shifted around. The convergent scheme to this related compound starts with the acylation of alanine (**35-1**) with butyryl chloride (**35-2**). The thus-produced amide (**35-3**) is then again acylated, this time with the half-acid chloride from ethyl oxalate in the presence of DMAP and pyridine to afford the intermediate (**35-4**). In the second arm of the scheme, the benzonitrile (**35-5**) is reacted with the aluminate (**35-6**), itself prepared from trimethyl aluminum and ammonium chloride, to form the imidate (**35-7**). Treatment of this intermediate with hydrazine leads to the replacement of one of the imidate nitrogen atoms by the reagent by an addition-elimination sequence to form (**35-8**). Condensation of this product with (**35-4**) leads to the formation of the triazine (**35-9**). Phosphorus oxychloride then closes the second ring

to afford (**35-10**). Reaction of this last intermediate with chlorosufonic acid affords the corresponding sulfonyl chloride. Treatment of this compound with *N*-ethyl piperazine forms the sulfonamide and thus **vardenafil** (**35-11**) [35,36].
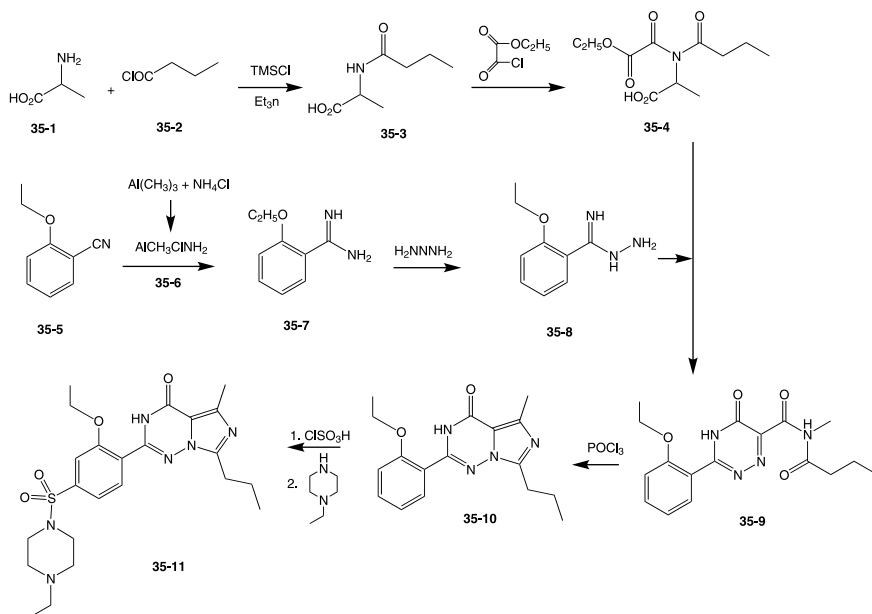
15.2.3.1.2. *Antimetabolites.* Because of their close structural relation to endogenous compounds involved in metabolism, purines have provided the nucleus for a sizeable number of antimetabolites used in the treatment of cancer. **Mercaptopurine**
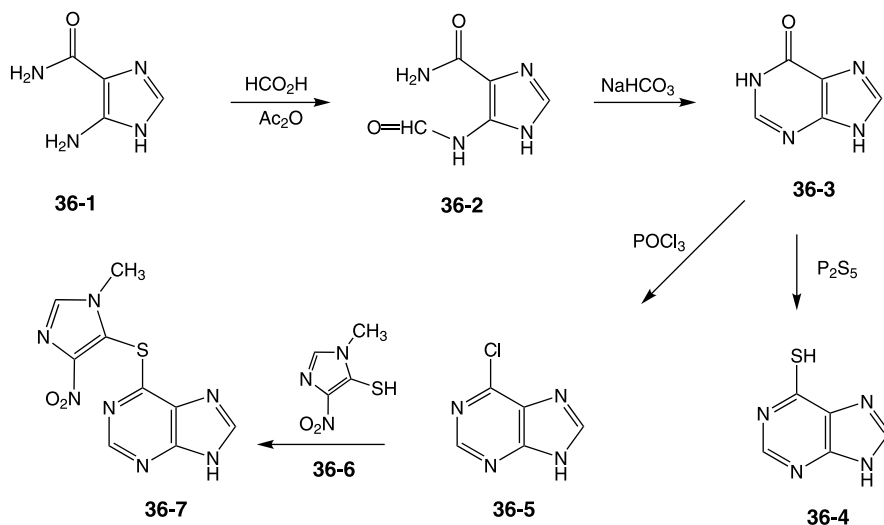
(**36-4**) was one of the first of this class of drugs to be used in the clinic. One synthesis for the starting purine, hypoxathine (**36-3**), starts with the formylation of aminoimidazole (**36-1**) with a mixture of formic acid and acetic anhydride to give (**36-2**). This cyclizes to hypoxanthine with the surprisingly mild base, sodium bicarbonate. Reaction of the product with phosphorus pentasulfide converts the carbonyl to its sulfur equivalent [37]. The product, **mercaptopurine** (**36-4**), is shown as its enol tautomer. Treatment of hypothanxine with phosphorus oxychloride converts that to the corresponding chloro derivative (**36-5**). The reactive chlorine atom is then displaced by a somewhat complex mercaptoimidazole (**36-6**) to give **azathioprine** (**36-7**) [38]. This somewhat more widely used drug is also employed as an immunosuppressant for organ implant procedures; the compound is in fact converted metabolically to **mercaptopurine**.

The pyrrazolopyrimidine **allopurinol** (**37-4**) was originally developed as a false substrate for the enzyme hypoxanthine oxidase, responsible for the fast metabolism of **mercaptopurine**. Use of the drug in the clinic revealed that the compound inhibits the metabolism of other xanthines in addition to hypoxanthine (**36-3**). This generalized xanthine oxidase inhibiting activity made this compound a useful drug for treating gout, as the symptoms of that disease are caused by an accumulation of uric acid, the end product of xanthine metabolism. One synthesis of this purine-like compound starts with addition-elimination of hydrazine to ethoxymethylene malononitrile (**37-1**); the initially formed adduct cyclizes under reaction conditions by addition of the terminal hydrazine nitrogen to the nitrile, to form the pyrrazole (**37-2**). The remaining cyano group is then hydrolyzed to the corresponding amide (**37-3**) with concentrated sulfuric acid. Reaction of that intermediate with formamide supplies the last carbon atom and leads to the formation of **allopurinol** (**37-4**) [39].
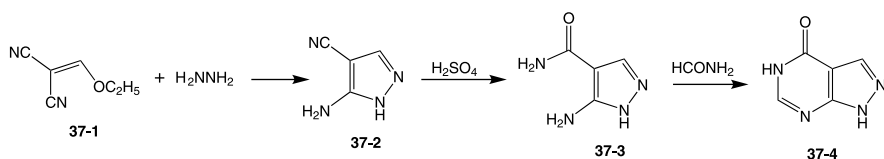
15.2.3.1.3. Glycosylated Compounds.

The rationale for the use of modified nucleosides for the treatment of cancer and viral disease relies on the hope that cancer cells or virally infected cells will mistake the modified compounds for the natural substrates and incorporate them into a metabolic pathway. The altered structure of the false substrate will, it is hoped, then bring that process to a halt and result in cell death.

While the cancer chemotherapeutic agent **fludarabine** (**38-7**) includes a sugar moiety characteristic of endogenous nucleotides, the hydroxyl group at position 3 in the furan ring, however, has the unnatural arabinose configuration. The presence of fluorine on the purine nucleus marks a further change from the natural purines. The synthesis starts with reaction of polyaminopyrimidine

(**38-1**) with formamide to form diaminopurine (**38-2**), which happens to be itself a metabolic inhibitor. The symmetry of the starting material permits only a single product. Treatment with acetic anhydride gives the corresponding di-acetylated derivative (**38-3**). The displacement of halogen in the fully benzylated arabinoside chloro-sugar (**38-4**) results in the glycosylation of the purine and the formation of (**38-5**). The amide groups are then removed by treatment of the product with a base. Reaction of the product with nitrous acid in the presence of fluoboric acid leads initially to the formation of the diazonium salt at position 2; this is displaced by fluorine to give the fluorinated derivative (**38-6**). The benzyl protecting groups are then cleaved by means of boron trichloride to afford **fludarabine** (**38-7**) [40].
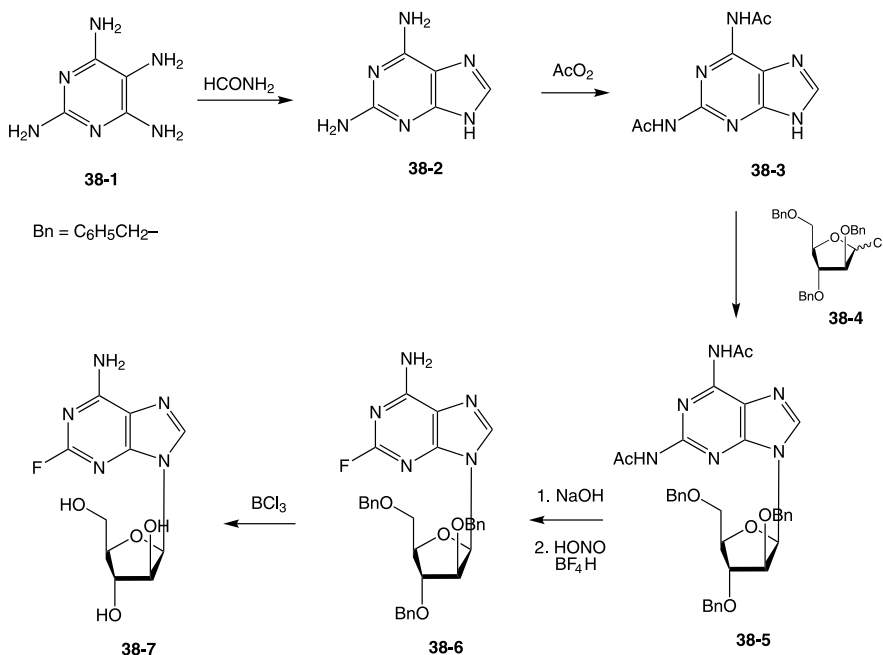
In a similar vein, reaction of the readily accessible xanthine (**39-1**) with the ubiquitous phosphorus oxychloride affords the enol chloride (**39-2**). Alkylation of the anion obtained from that product with a base with the chloro deoxy sugar (**39-3**) leads to the glycosylated product (**39-4**). Treatment with ammonia selectively replaces the halogen at the 6 position. The protecting groups on the sugar are cleaved in the course of the reaction to afford **cladribine** (**39-4**) [41].

Tol = 4-CH₃C₆H₄CH₂
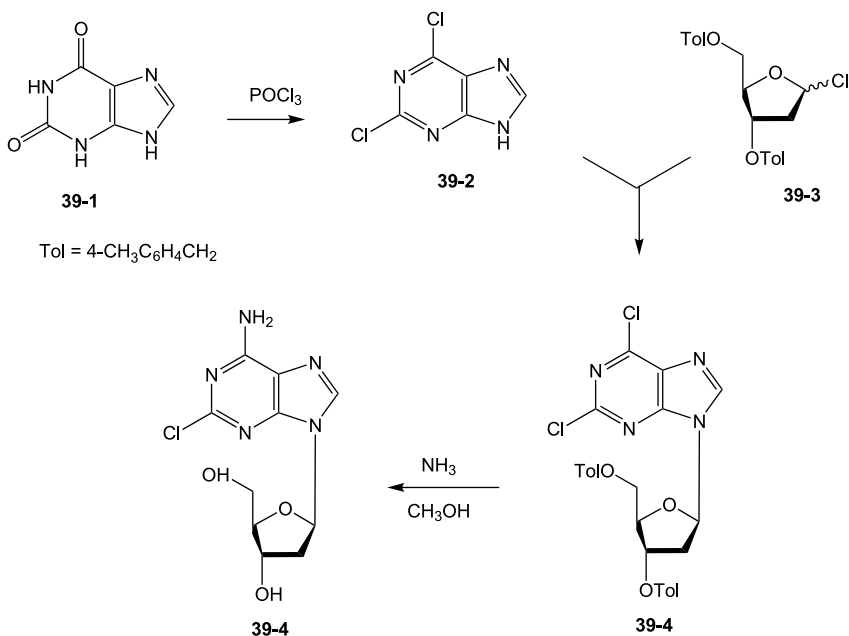
Research on compounds that interact with adenosine A1 receptors has focused on agonists with structures based on adenosine itself as agents that will overcome responses due to inappropriate excitation such as tachycardia and some arrhythmias. Replacement of one of the hydrogen atoms on the exocyclic amine in adenosine by a tetrahydrofuryl group provides an effective A1 adenosine agonist. Preparation of this fragment as a single enantiomer starts with a modern version of the Curtius reaction.
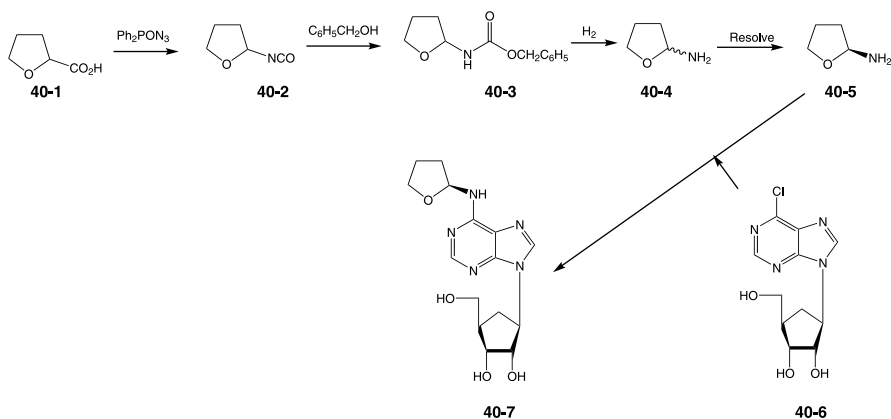
Thus, reaction of tetrahydrofuroic acid (**40-1**) with triphenylphosphoryl azide leads to isocyanate (**40-2**). Treatment of this intermediate with benzyl alcohol then affords the corresponding carbamate (**40-3**). Catalytic hydrogenation removes the benzyloxy group, leading to the free primary amine. That product is then resolved by way of its camphorsulfonyl salt to afford (**40-5**). Reaction of this intermediate with desamino chloroadenosine (**40-6**) affords **tecadenoson** (**40-7**) [42].

Another approach to preparing A1 adenosine receptor agonists involves converting the hydroxymethyl group on the sugar moiety to an amide in addition to adding a substituent to the amine of adenosine. The starting material (**41-2**) is arguably obtainable by oxidation of inosine acetonide (**41-1**), followed by acetylation of the hydrolysis product. Reaction of the acid with thionyl chloride followed by ethanol affords the corresponding ethyl ester (**41-3**). The ring oxygen on this intermediate is next replaced by chlorine by means of phosphorus oxychloride to yield (**41-4**). Reaction of this last with cyclopentylamine displaces the halogen to form the cyclopentylamino derivative (**41-5**). Treatment with triethylamine under somewhat more strenuous conditions effects the ester-amide interchange to form the amide; the acetyl protecting groups are cleaved under those reaction conditions. There is thus obtained the A1 adenosine receptors agonist **selodenoson** (**41-6**) [43].
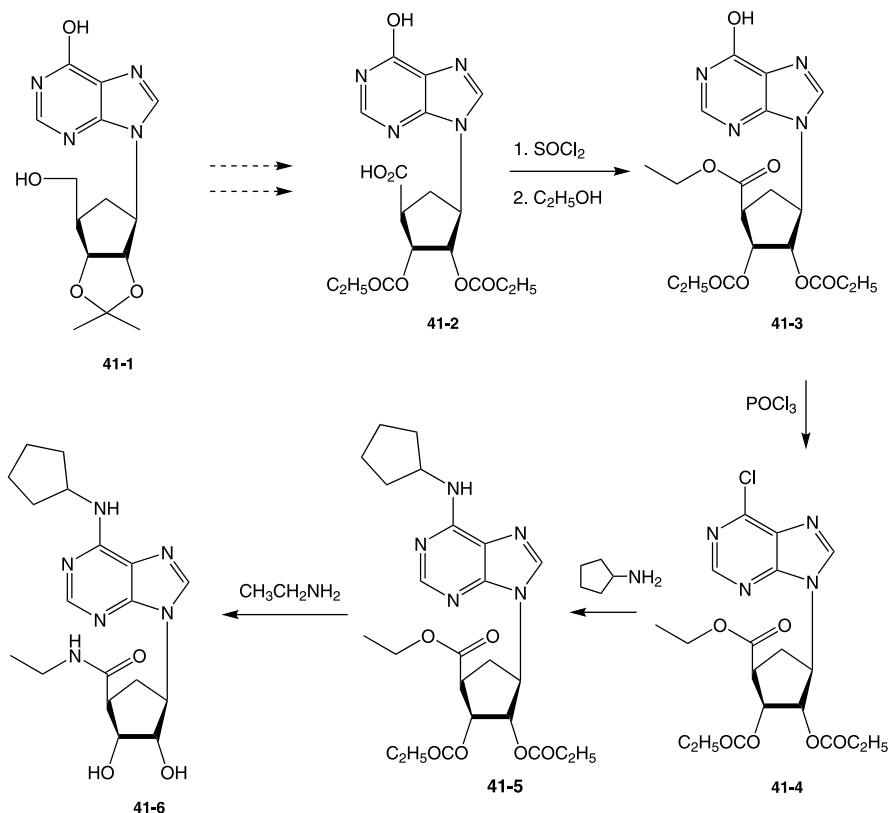
The use of false substrates has met particular success with antiviral agents that consist of purines glycosylated with open chain sugar surrogates. The anti-herpes drug **acyclovir** (**42-6**) [28] was the first of its type to gain approval [44]. In one of the more recent syntheses, the side chain synthon (**42-4**) is prepared by acylation of dioxolane (**42-3**) with acetyl chloride to give the ring opened product. Reaction of that with the diacetate (**42-2**) from guanine (**42-1**) in the presence of *p*-toluene-sulfonic acid leads to the glycoside-like derivative (**42-5**) by exchange of the acetal with purine nitrogen. Treatment of that intermediate with methanolic ammonia at ambient temperature affords **acyclovir** (**42-6**) [45].
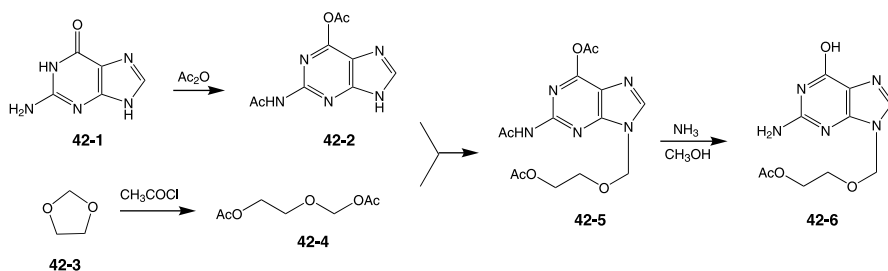
The addition of a hydroxymethyl group, which presumably increases the resemblance to a sugar, gives a compound that is effective mainly against cytomegalo viruses (CMV). The protected triol (**42-3**) for this compound is prepared by a stepwise reaction of epichlorohydrin (**43-1**) with two equivalents of the anion from benzyl alcohol; in a β-blocker-like sequence the first equivalent leads to a glycidic ether; this opens to (**42-3**) with a second equivalent. Reaction of this intermediate with formaldehyde and hydrogen chloride gives the chloromethyl ether (**43-4**). Treatment of the *tris*-trimethylsilyl derivative (**43-5**) from guanine with that reactive intermediate leads to the glycoside-like intermediate (**43-6**).
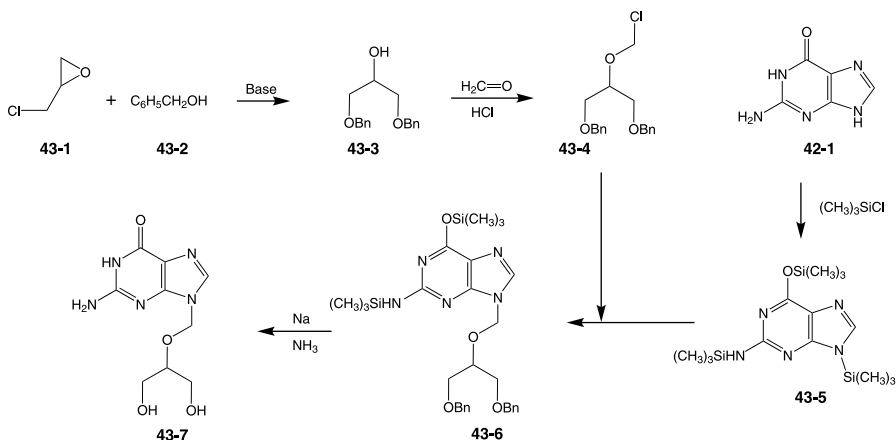
The benzyl groups arethen removed reductively by means of sodium in liquid ammonia to afford **ganciclovir** (**43-7**) [46].

Another compound with a truncated sugar in which the hydroxyls are located on a linear side chain has demonstrated good activity against varicela zoster, the cause of chicken pox and shingles. The scheme for preparing this compound differs from the preceding example in that the pendant group is attached via a Michael reaction. Thus reaction of the purine (**44-1**) with glutarate (**44-2**) in the presence of a base leads to the conjugate addition of purine nitrogen to the double bond (**44-3**). Treatment with lithium borohydride then reduces the carboxyl groups to afford diol (**44-4**) as a mixture of enatiomers. Reaction with ammonia then introduces the requisite amine by replacing chlorine on the purine to afford the diamine (**44-5**). That intermediate is treated with the enzyme adenosine deaminase immobilized on a solid support. The enzyme reacts preferentially with the isomer in which the stereochemistry of the secondary hydroxyl group more closely resembles that in the furanoside in a natural nucleoside converting the amine at the 4 position to a hydroxyl group. Separation of that from the unreacted starting material affords **omaciclovir** (**44-6**) [47].
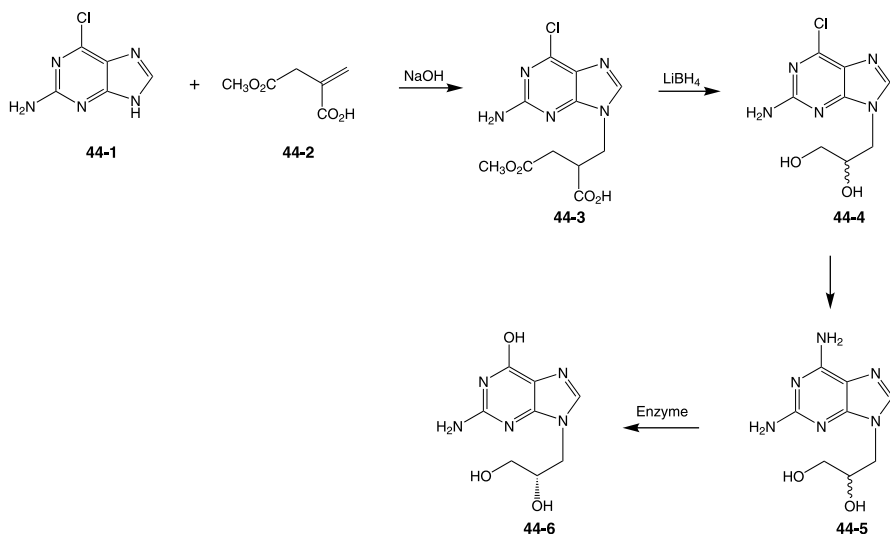
An alternate approach comprises replacing the pendant sugar by either a carbocyclic or a heterocyclic ring. The enantioselective synthesis starts by formation of the imide (**45-3**) by reaction of the aion from the chiral auxiliary (**45-2**), derived from *S*-phenylalaninol and the pentene ester (**45-1**). Treatment of the product with triethyl amine and the trifalate from dibutylboronic acid leads to the transient enol borate (**45-4**). Aldol addition of that enol to acrolein proceeds stereospecifically to the alcohol (**45-5**) due to the transfer of chirality from the chiral auxiliary.

Exposure of the product to the ruthenium complex leads to an olefin metathesis reaction. The two pendant ethylene moieties exchange with the formation of the cyclopentenone (**45-6**) and the loss of ethylene. Sterochemistry is preserved as the reaction involves only nonchiral moieties. Reduction of the product with lithium borohydride leads to a carbinolamine that cleaves under reaction conditions. Reduction of the adjacent ketone affords the corresponding diol that is then treated with acetic anhydride to yield diacetate (**45-7**). Palladium catalyzed coupling of this last with the purine (**45-8**) in this case involves an allylic rearrangement. The reaction can be rationalized by an attack of nitrogen on the terminus of the allylic system; the double bond then shifts over and expels the acetate group, affording the coupling product (**45-9**). Saponification completes the synthesis of the HIV reverse transcriptase inhibitor **abacavir** (**45-10**) [48].
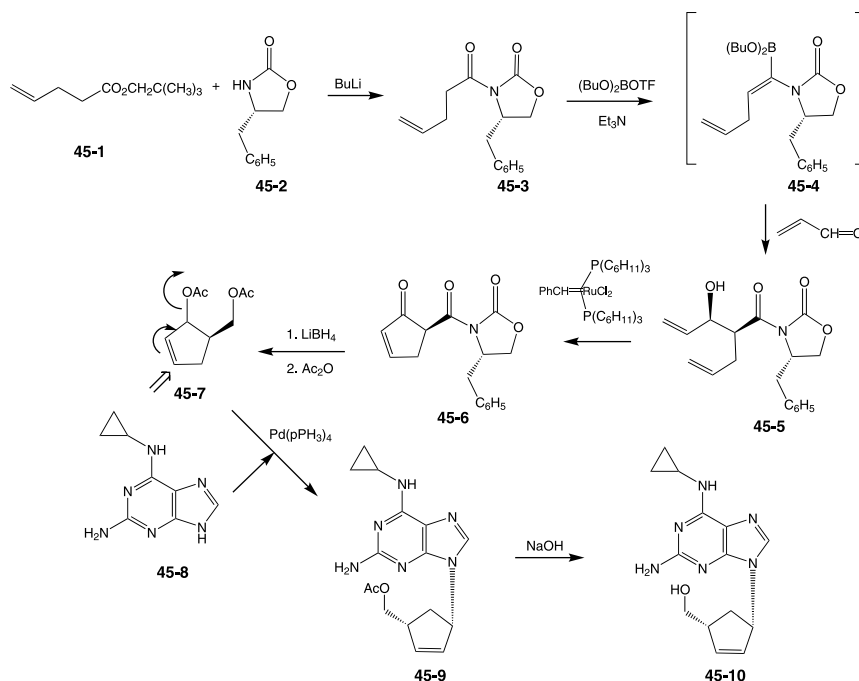
The insertion of a second oxygen atom in a sugar furanose ring in essence converts that moiety to an acetal. This modification leads to another false substrate for viral reverse transcriptase. Glycosilation of the silylated purine (**46-1**) with chiral dioxolane (**46-2**) prepared in several steps from anhydromannose in the presence of ammonium nitrate affords the coupling product as a mixture of anomers (**46-3**). The mixture of products is then separated on a chromatographic column. The desired diastereomer (**46-3**) is reacted with ammonia to afford the product (**46-4**)

from the replacement of fluorine. Reaction of this intermediate with ammonia under more strenuous conditions replaces chlorine (**46-5**). Treatment of this last with a fluoride ion removes the silyl protecting group to afford the reverse transcriptase inhibitor **amdoxovir** (**46-6**) [49].

15.2.3.1.4. *Miscellaneous Compounds.*

15.2.3.1.4. *Miscellaneous Compounds.* Heterocycles related to 2-amino-pyrimidine have been investigated as diuretic agents because they tend to be less potassium depleting than the classical sulfonamides. The six-membered ring in one of these examples, **bemitradine** (**47-9**), is formed in a typical pyrimidine synthesis by the condensation of ketoester (**47-1**) with guanidine. The amino group in the product (**47-2**), shown as its keto tautomer, is then protected as its formamide (**47-3**). Reaction with phosphorus oxychloride converts the enol to the chloro derivative (**47-4**). The replacement of halogen by hydrazine then affords the key intermediate (**47-5**).The fused five-membered ring is formed by condensation with ethyl orthoformate to give the pyrrazolopyrimidine (**47-6**). This rearranges to the isomeric compound (**47-9**) on heating. The sequence can be rationalized by assuming an initial fragmentation of the pyrimidine bond to give the intermediate (**47-7**); simple rotation of the triazole moiety leads to (**47-8**). Reclosure of the ring will then afford the observed product, **bemitradine** (**47-9**) [50].

The starting material (**48-1**) for a pyrrazolopyridazine can be obtained by treating the corresponding enol, which is simply the condensation product of methylmaleic anhydride and hydrazine, with phosphorus oxychloride. Reaction with piperazine leads to the displacement of the sterically more accessible chlorine to afford the alkylation product (**48-2**). Treatment with hydrazine leads to the replacement of the remaining halogen and the formation of (**48-3**). The missing carbon is, in this case, supplied by formamide to afford **zindotrine** (**48-4**) [51], a compound that shows activity as a bronchodilator.
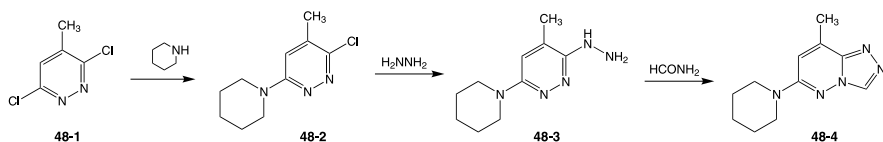
The route to two adenines susbtituted on the imidazole ring relies on incorporating that substituent prior to closing the fused five-membered ring. The first several steps in the synthesis of the natural product from mushrooms, **eritadenine** (**49-7**), comprise constructing the requisite chiral side chain starting from the butyrolactone (**49-1**), which is obtained by degradation of a sugar. Reaction with the sodium phthalimide

(Phth-) leads to a ring opening of the reactive lactone with the displacement of the ester oxygen by nitrogen; the phthalimide group is then removed by treatment of the intermediate with hydrazine to afford (**49-2**). The amine group is allowed to displace chlorine in the 2-amino-4-chloro-3-nitropyrimidine (**49-3**) to afford (**49-4**). Catalytic hydrogenation of that intermediate leads to the reduction of the nitro group and the formation of triamine (**49-5**). Acylation of this triamine with formic acid proceeds at the more basic of those groups. The acetonide protecting group hydrolyzes under reaction conditions to give the observed product, amide (**49-6**). This intermediate cyclizes to the desired imidazole on reaction with a base to give a purine. There is thus obtained **eritadenine** (**49-7**), a compound that showed hypolipidemic activity in various test systems [52].
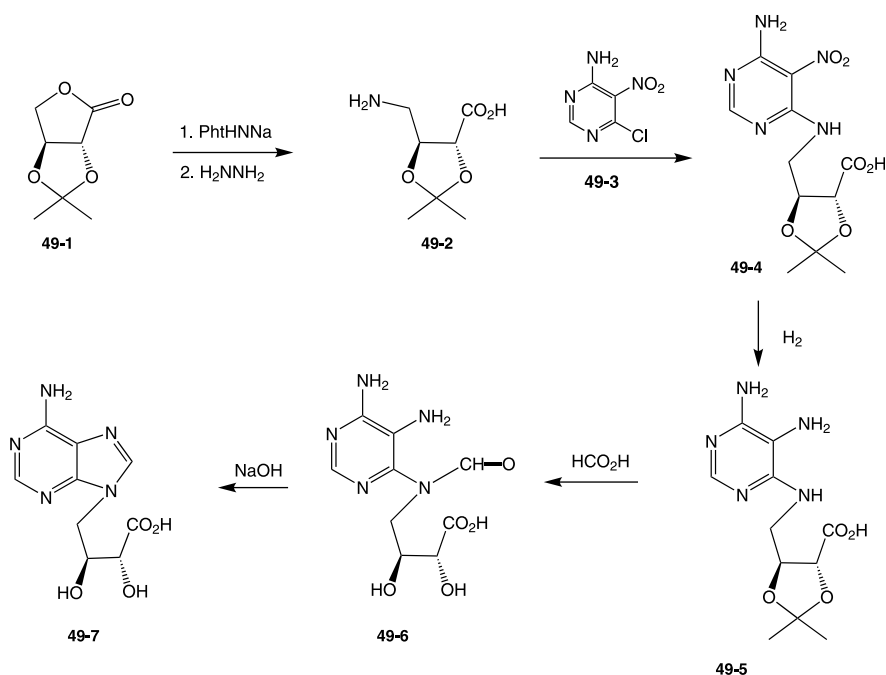
Treatment of the symmetrical triaminopyrimidine (**50-1**) with sulfuryl chloride ties up the two adjacent amines in a thiadiazole ring, protecting those groups from attacks in subsequent reactions. Reaction of the product (**50-2**) with *ortho* difluorinated benzylamine (**50-3**) results in the replacement of the pyrimidine amino group by that in the reagent most likely by an addition-elimination sequence to afford (**50-4**). That amino group is then converted to the formamide (**50-5**) with formic acid. Exposure of the product to Raney nickel leads to a loss of sulfur and the formation of the transient intermediate (**50-6**). This cyclizes to a purine

under reaction conditions to yield **arprinocid** (**50-7**) [53], a compound used as a poultry coccidiostat.
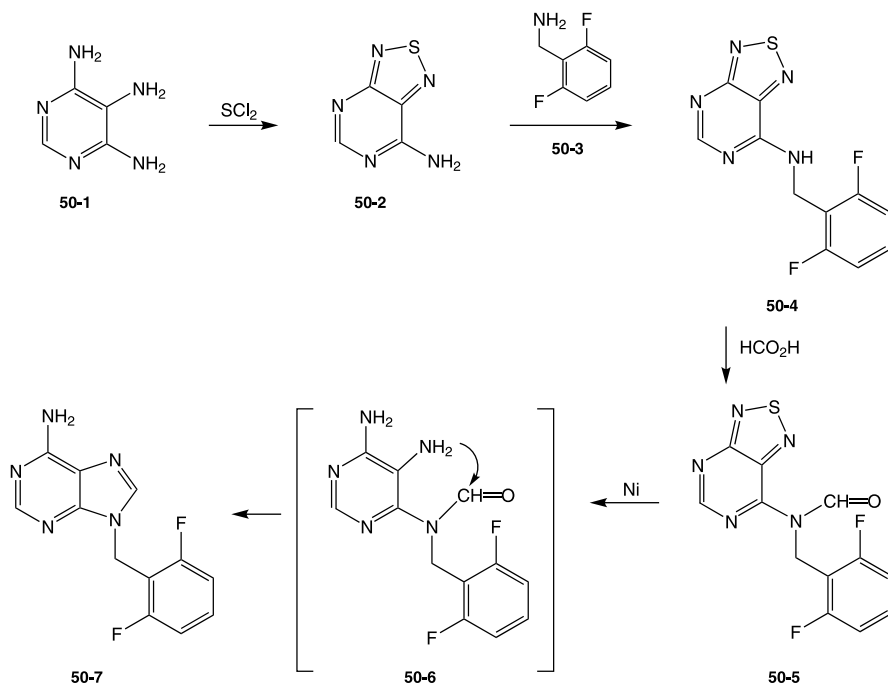
15.3. TWO FUSED SIX-MEMBERED RINGS

15.3.1. Compounds Related to Methotrexate

The pivotal role of folates in purine synthesis and consequently cell growth has been addressed earlier, as has the use of folate antagonists as cytotoxic agents.

Follic Acid
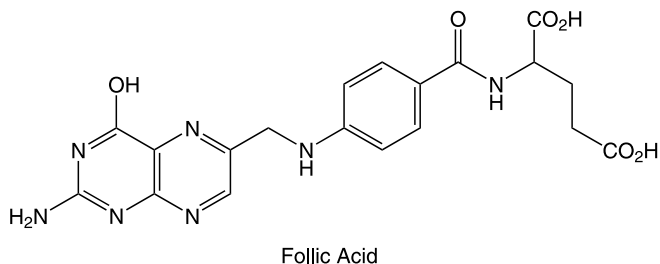
Methotrexate (**53-6**), one of the first modified pteridines investigated as a folate antagonist, is still used quite extensively in the chemotherapy of cancer and to a minor extent in other indications calling for cytotoxic agents.

One synthesis for this compound involves the three-component condensation of polyamino pyrimidine (**52-1**), *N*-methylglutamyl-*para*-aminobenzoic acid (**52-4**), and 2,3-dibromopropion-aldehyde (**52-2**) in the presence of potassium iodide. The initial step can be envisaged as condensing the aldehyde with the aminopyrimidine to give an intermediate such as (**52-3**), assuming that the reaction starts with the formation of the pteridine. Alkylation of the amine on the PABA moiety by bromide (**52-3**) will then lead to the observed product (**52-5**). The reversed order of these reaction, starting with the alkylation of the amine on PABA by the bromoaldehyde, cannot, however, be ruled out. Air oxidation of the dihydro ring in the initial product completes the synthesis of **methotrexate** (**52-6**) [54]. It is of note in passing that initial supplies of this drug comprised compounds of only roughly 60% purity, the reasonably pure drug not being available until the mid-1980s.
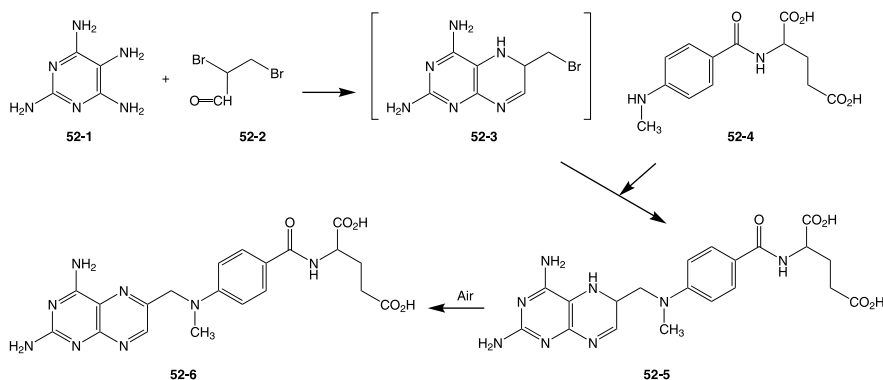
Replacement of nitrogen *para* to the carboxyl on PABA by a methylene group leads to a compound that has one less site for potential metabolic cleavage. Reaction of the bromomethyl pteridine (**53-1**), obtainable by suitable modification of the scheme above, with triphenylphosphine leads to the phosphonium salt (**53-2**). Condensation of the ylide from the treatment of the salt with butyl lithium with *para*-carbethoxypropiophenone (**53-3**) gives the coupling product (**53-4**). The superfluous double bond is then reduced by catalytic hydrogenation; the pyrazine ring is reduced as well in an undesired side reaction to give (**53-5**). Oxidation with hydrogen peroxide restores that ring to its fully saturated form (**53-6**). Saponification of the product (**53-6**) with a base then gives the corresponding acid (**53-7**). Dicyclohexyl carbodiimide (DCC) mediated coupling with diethyl glutamate (**53-8**) gives the desired amide (**53-9**). A second round of saponification affords the free carboxylic acid and thus **edatrexate** (**53-10**) [55].
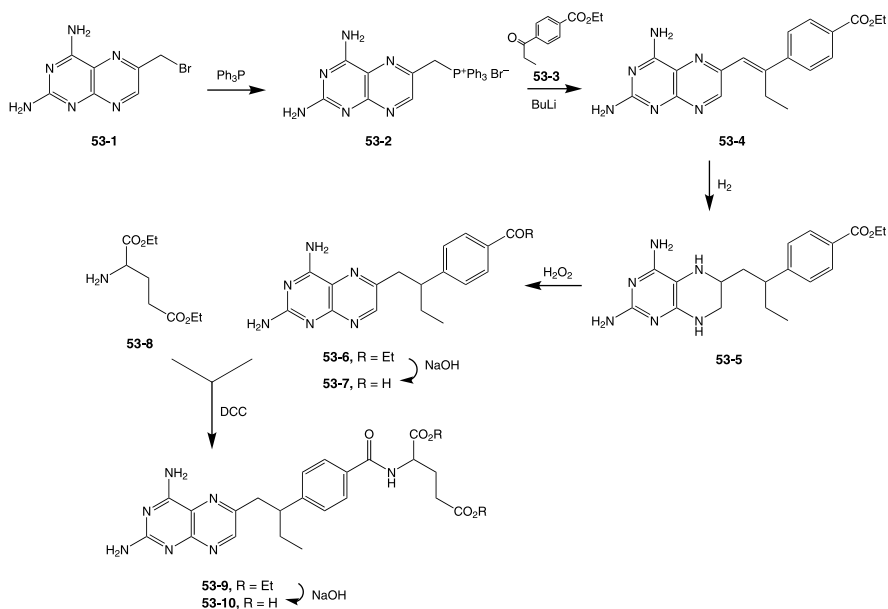
The synthesis of the analogue in which one of the pteridine nitrogen atoms is omitted starts with the reaction of aminopyrimidone (**54-1**) with 2-bromomalonalde-hyde (**54-2**). This condensation may be envisoned as involving an initial condensation
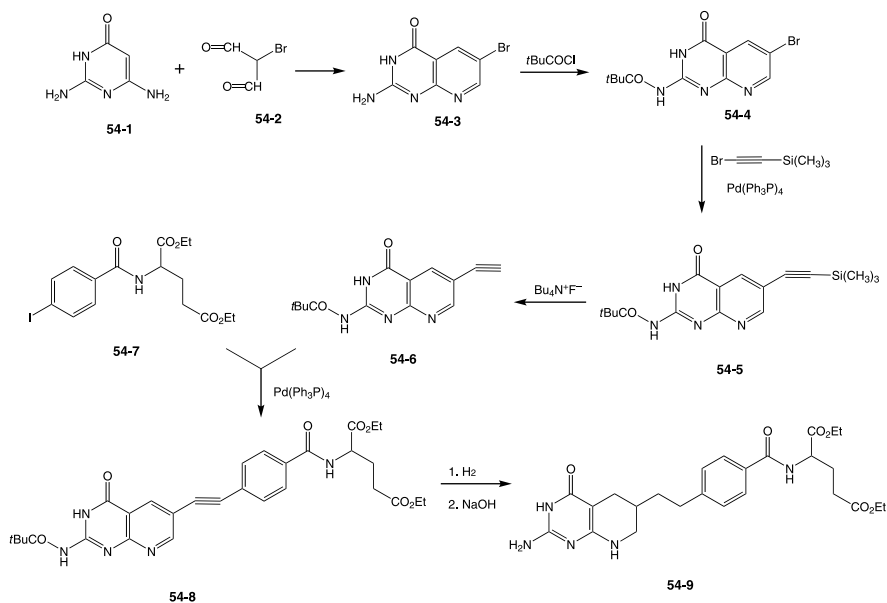
of the aldehyde with the electron-rich enamide carbon; imine formation then completes the formation of the fused pyridine ring to afford the product (**54-3**). The amine at position 2 is protected as its pivaloyl amide (**54-4**) by reaction with pivaloyl chloride. Palladium catalyzed coupling of halogen in the intermediate with mono-trimethylsilyl acetylene gives the product (**54-5**) that now contains the side chain carbon atoms. The silyl protecting group is then removed by exposure of the compound to fluorine anions. The surrogate PABA ring is then added in a second palladium catalyzed coupling step. Thus, reaction of the acetylene (**54-6**) with iodobenzene (**54-7**) leads to the intermediate (**54-8**), which now includes the complete carbon skeleton. The acetylene is then reduced by catalytic hydrogenation; the pyridine ring is reduced to its tetrahydro derivative in the same step. Saponification removes the ethyl esters as well as the pivaloyl amide to give the folate antagonist **lometrexol** (**54-9**) [56].

A compound lacking the glutamide residue still, surprisingly, shows considerable antifolate activity. The synthesis of this agent starts with Knoevnagel-like condensation of benzaldehyde (**55-1**) with ethyl acetoacetate. Catalytic reduction of the product gives the substituted acetoacetate (**55-2**). Reaction of the product with aminopyrimidine (**55-3**) follows a similar course to that discussed above. The product from this reaction (**55-4**) in this case, however, is an amide due to the higher oxidation state of one of the carbonyl groups. The sequence for reducing that function starts by reaction with phosphorus oxyxchloride to give the enol chloride (**55-5**). Hydrogenolysis of the product over palladium removes the halogen to afford **piritrexim** (**55-6**) [57].
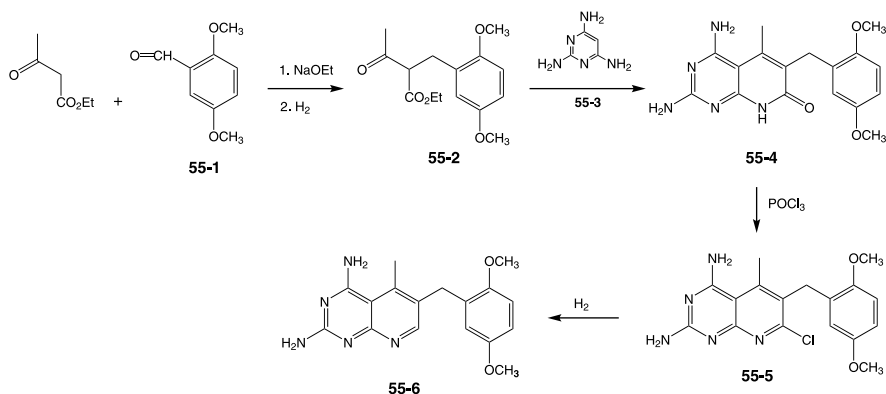
Yet another cytotoxic agent that lacks the glutamate side chain illustrates the breadth of the SAR in this series. It is of note that the three nitrogen atoms in the fused six-membered ring system are disposed so as to form a pyridopyrazine rather than a pyrimidopyrimidine, as in piritrexim. The observation that this agent also inhibits tubulin may play an additional role in its activity. Nucleophylic aromatic

displacement of chlorine in the highly substituted pyridine (**56-1**) by the amine in chiral pseudoephedrine (**56-2**) leads to the coupled secondary amine (**56-3**). The alcohol is next oxidized to the corresponding ketone (**56-4**) by means of chromium trioxide in acetic acid. Raney nickel then serves to reduce the nitro group to an amine; reaction of the newly formed function with the side chain carbonyl forms an imine and closes the ring. There is thus obtained the antineoplastic agent **mivobulin** (**56-6**) [58].
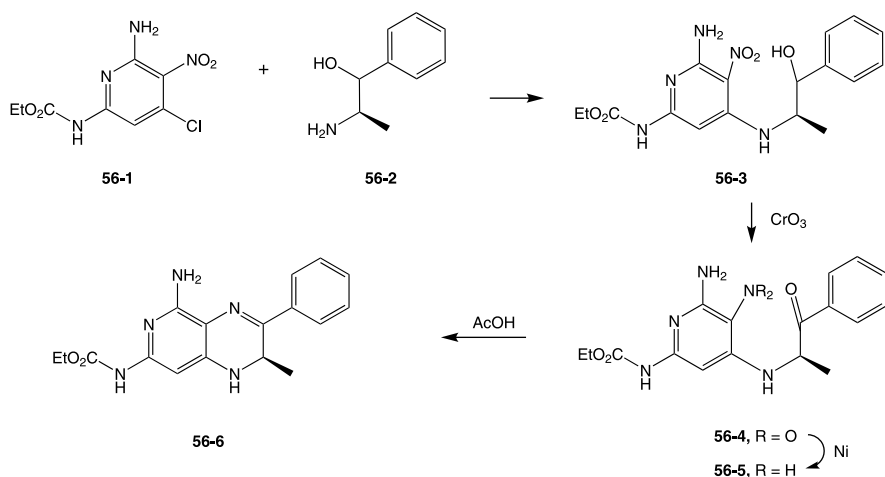
15.3.2. Other Fused Heterocyclic Compounds

The compounds that follow, in contrast to those in the preceding section, do not have any unifying theme, be it biological or chemical. They are consequently considered simply in order of the increasing number of heteroatoms present in the bicyclic nucleus.

The well-established antiarrhythmic agent **disopyramide** (**57-1**) comprises the starting material for a cyclized version of that drug that is somewhat more potent than the parent. Catalytic hydrogenation of (**57-1**) in the presence of an acid results in the selective reduction of the pyridine ring to give the corresponding piperidine.
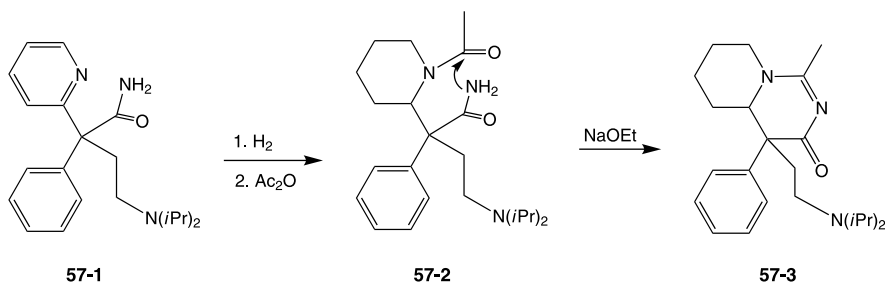
Treatment of the intermediate with acetic anhydride affords the acetamide (**57-2**). Reaction of the product with a base leads to an attack of the nitrogen on the secondary side chain amide on the newly introduced amide carbonyl with the formation of the cyclic amidine. There is thus obtained the antiarrhythmic agent **actisomide** (**57-3**) [59].

Pyridones form an integral part of the pharmacophore in the cardiotonic agents **amrinone** and **milrenone** (see Chapter 9). The biologic activity is retained when the ring is fused onto pyridine. Condensation of the amino-enamine (**58-1**) from acetylacetone with the ethyl ester of propargilic acid (**58-2**) can be visualized as proceeding through an intial conjugate addition of the enamine to the triple bond to give a transient intermediate such as (**58-3**). Ester-amide interchange will then lead to the cyclization of the observed product, pyridone (**58-4**). The methyl group on that ring is activated by both the adjacent enamide and vinyl ketone. Reaction with Bredereck's reagent thus gives the aminoformylated derivative (**58-5**). Treatment with ammonium acetate probably results in the initial displacement of the dimethyla- mino group by ammonia to give a primary enamine; this then closes to a pyridine ring in a Hantsch-like reaction. There is thus obtained **medorinone** (**58-6**) [60].
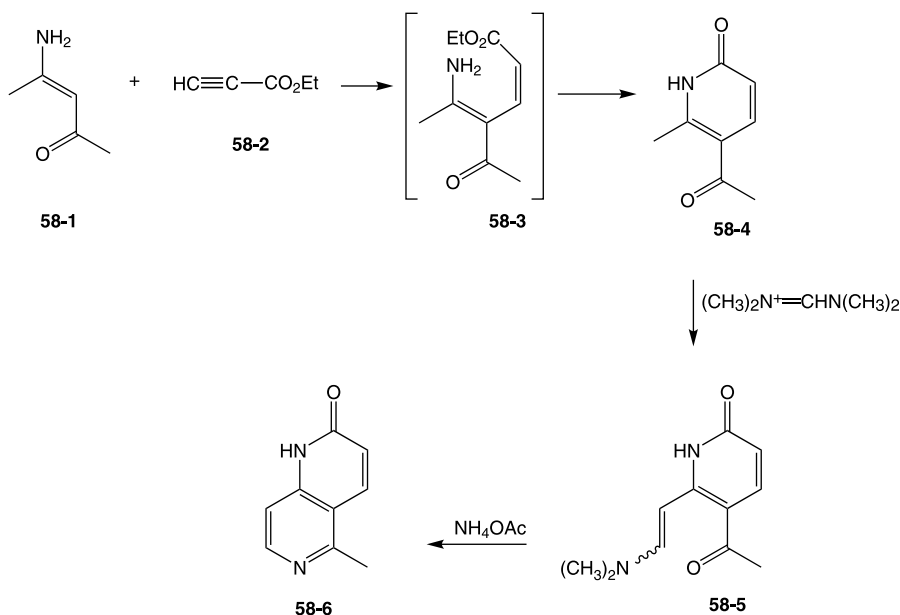
The general method used to form the 4-pyridone ring that characterizes the quinolone antibiotics can also be used to form such rings fused onto other hetero- cyles. Addition-elimination of aminopicoline (**59-1**) with ethoxymethylenecyano- acetate (**59-2**) gives the adduct (**59-3**) (no stereochemistry should be ascribed to the depiction). This compound cyclizes to the fused heterocycle (**59-4**) on heating in diphenyl ether. The presence of a methyl group on the other *ortho* position renders

moot the question of C versus N cyclization. Reaction of the product with sodium azide converts the nitrile to a tetrazole [61]. There is thus obtained **pemirolast** (**59-5**), one of a sizeable group of tetrazoles that show mediator release inhibiting and thus antiallergic activity in experimental animals.
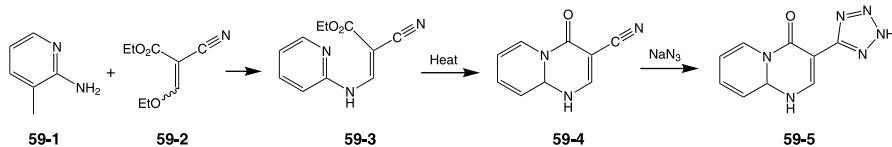
A compound with a markedly different structure from the benzodiazepines and the subsequent drugs of the "spirones" class had shown promising anxiolytic activity in animal models. The synthesis starts by conversion of the pyridine dicarboxylic acid (**60-1**) to its acid chloride with thionyl chloride; reaction with methanol then affords the ester (**60-2**). Catalytic hydrogenation serves to reduce the pyridine ring to a piperidine of undefined stereochemistry (**60-3**). Alkylation of this intermediate with chloroacetonitrile affords (**60-4**). Treatment of that intermediate with Raney nickel reduces the cyano group to the corresponding primary amine; this product then undergoes an internal ester-amine interchange to yield the cyclized amide (**60-5**). Lithium aluminum hydride serves to reduce the amide to an amine; the ester on the other ring is converted to a carbinol in the process, affording the amino alcohol (**60-6**). The basic function is next alkylated with 2-chloropyrimidine (**60-7**). Reaction of the alcohol in (**60-8**) with methanesulfonyl chloride leads to the mesylate; that group
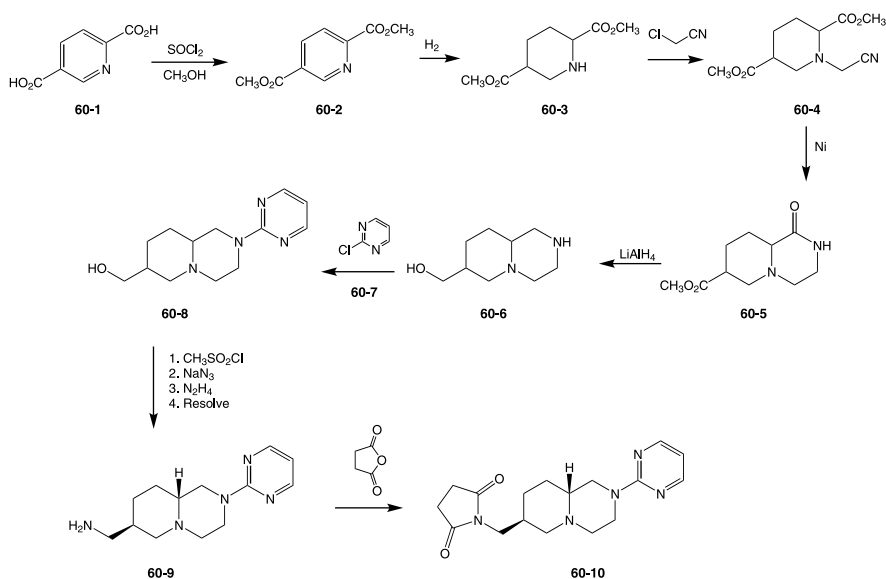
is next displaced by means of sodium azide and the newly introduce azide group reduced to the primary amine. Resolution of this last product as its mandelate salt then yields (**60-9**) as a single enantiomer. Reaction of that product with succinic anhydride converts the pendant amine to a succinimide, affording the anxiolytic agent **sunepitron** (**60-10**) [62].

The first of what became a large collection of quinolone antibiotics, **nalidixic acid** (Chapter 11), in fact consisted of a pyridone fused onto a pyridine ring. Retention of activity in this series in the face of an extra nitrogen atom in the fused ring is thus not completely unexpected. Construction of the starting material for an aza analogue begins by displacement by pyrrolidine of the more labile chlorine in dichloropyrimi-dine (**61-1**) to give (**61-2**). Displacement of the remaining halogen by ammonia gives the primary amine (**61-3**). The quinolone ring is then fused in the usual way by addition-elimination with ethoxymethylenemalonate (EMME) followed by thermal ring closure to give (**61-4**). The secondary amine on the pyrimidone ring is then alkylated with ethyl iodide (**61-5**). Saponification of the ester completes the synthesis of the antibacterial agent **piromidic acid** (**61-6**) [63].
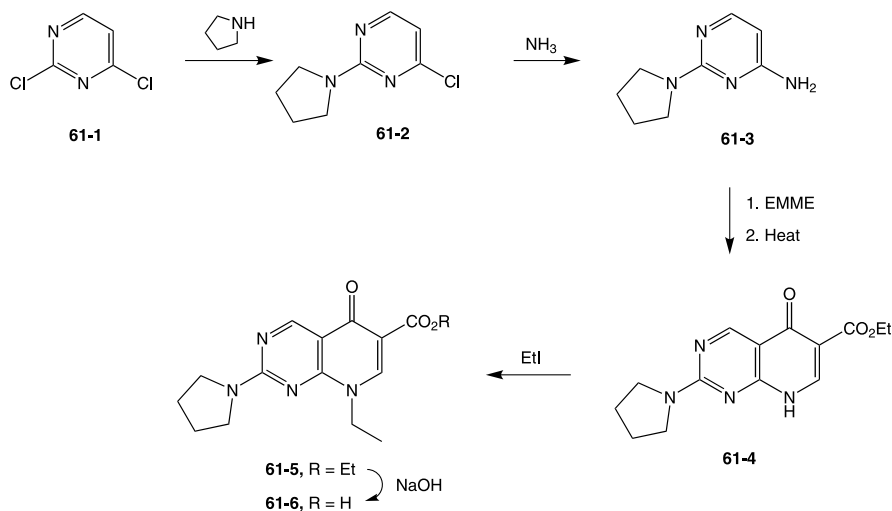
Displacement of the very labile chlorine on chloronitropyridine (**62-1**) with the mono ethyl urethane from hydrazine gives the substitution product. The protecting group is then removed by successive saponification and decarboxylation of the thus-formed carbamic acid to give the corresponding free hydrazine (**62-2**). Catalytic hydrogenation then reduces the nitro to afford the bidendate derivative (**62-3**). Condensation of that with phenylacetic acid probably leads first to the reaction with the more basic terminal hydrazine nitrogen to form a hydrazide; this then cyclizes to the amidine (**62-5**). Dehydrogenation with manganese dioxide completes the synthesis of the antifungal agent **triafungin** (**62-6**) [64].
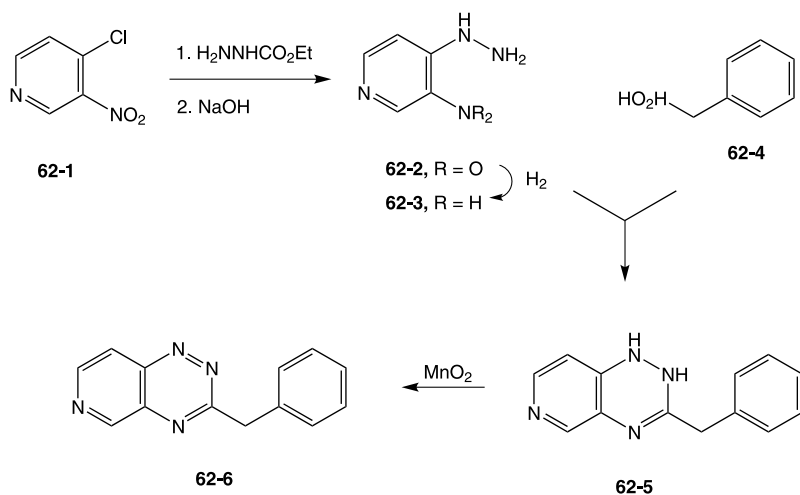
One of the first so-called potassium sparing, nonthiazide diuretic agents contains a pterdine nucleus. This is reflected in the use of the pterdine staring material *tetra*-aminopyrimidine (**38-2**) in the synthesis. Thus, reaction of benzaldehyde with that polyamine and potassium cyanide leads to the formation of the cyanohydrin-like α-aminonitrile (**63-2**) from reaction of the most basic amino group. Treatment of the intermediate with a base leads to the addition of the amine to the nitrile to give the dihydropteridine (**63-3**). Simple exposure to air leads to dehydrogenation and the formation of **triamterine (63-4)** [65].
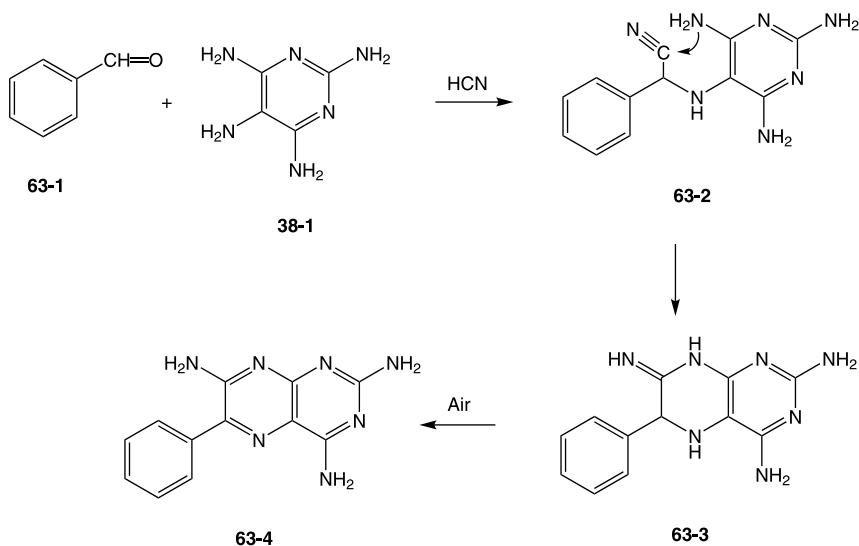
15.4. HETERODIAZEPINES

The interchangeability of unsaturated rings in biologically active compounds is illustrated particularly well in compounds related to the anxiolytic agent **chlordiazepoxide** (Chapter 12). Analogues in which the fused benzene ring in the prototype benzodiazepines is replaced by heterocycles such as pyrrazole or thiophene show activity that is usually equivalent or superior to the prototype. The chemistry used to prepare these analogues quite closely parallels that used to prepare the benzene fused compounds. In one of the simpler examples, Friedel–Crafts acylation of chloropyrrazole (**64-1**) with *meta*-chlorobenzoyl chloride (**64-2**) affords the pyrazolophenone (**64-3**). The initial step in the reaction of that compound with ethylene diamine likely involves the displacement of halogen in the heterocycle by one of the amino groups in the reagent. Imine formation with the second amino group closes the seven-membered ring to afford the anxiolytic agent **zometapine** (**64-4**) [66].
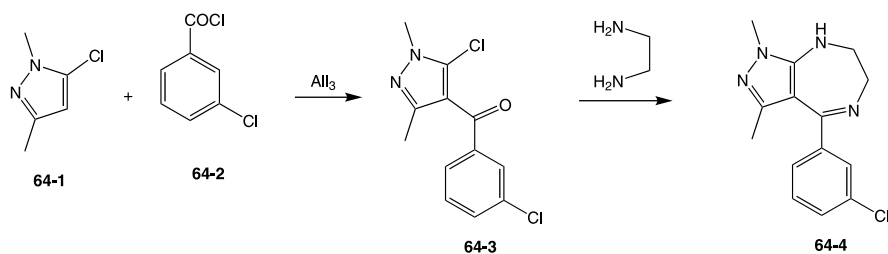
Reaction of the pyrazole (**65-1**) with nitric and sulfuric acids results in the formation of the nitro derivative (**65-2**). The carboxylic acid group is then converted
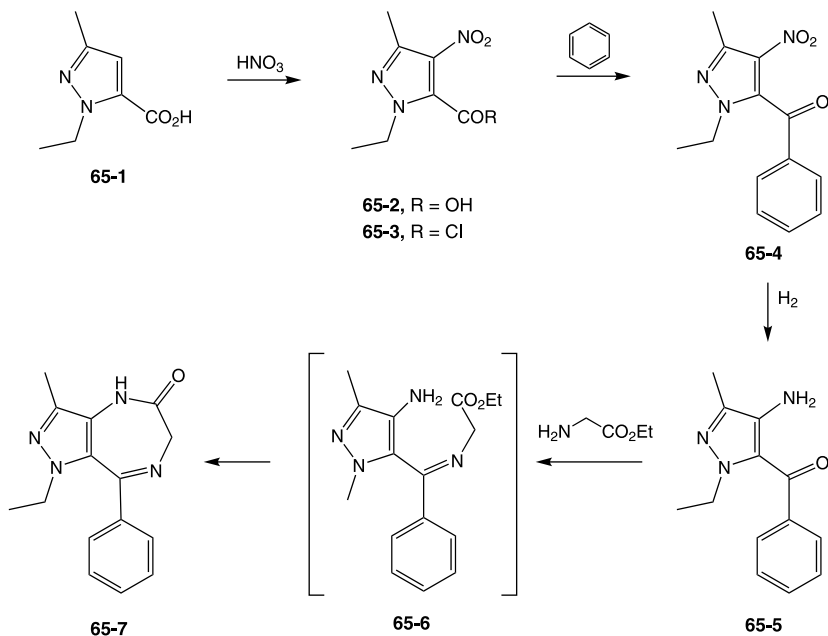
to its acid chloride (**65-3**) and this used to acylate benzene in a Friedel–Crafts reaction. The nitro group in the resulting pyrrazolophenone (**65-4**) is then reduced to give the amine (**65-5**). Following classical benzodiazepine chemistry, this amino-benzophenone counterpart is then treated with ethyl glycinate in pyridine. The hypothetical initially formed imine (**65-6**) cyclizes to the diazepinone ring under reaction conditions. There is thus obtained the minor tranquilizer **ripazepam** (**65-7**) [67].

Another common approach to the seven-membered ring involves introducing nitrogen at a late stage. The requisite phenone (**66-3**) is obtained by Friedel-Craftsacylation of aminopyrrazole (**66-1**) with *ortho*-fluorobenzoyl chloride (**66-2**). The acetamide protecting group is then removed and the thus-obtained secondary amine acylated with chloroacetyl chloride to give the chloroacetamide (**66-4**). Nitrogen is then introduced by displacement of the reactive chlorine with sodium azide. Catalytic hydrogenation reduces the azide to a primary amine; the resulting product (**66-5**) spontaneously cyclizes to form an azepinone to give **zolazepam** (**66-6**) [68].
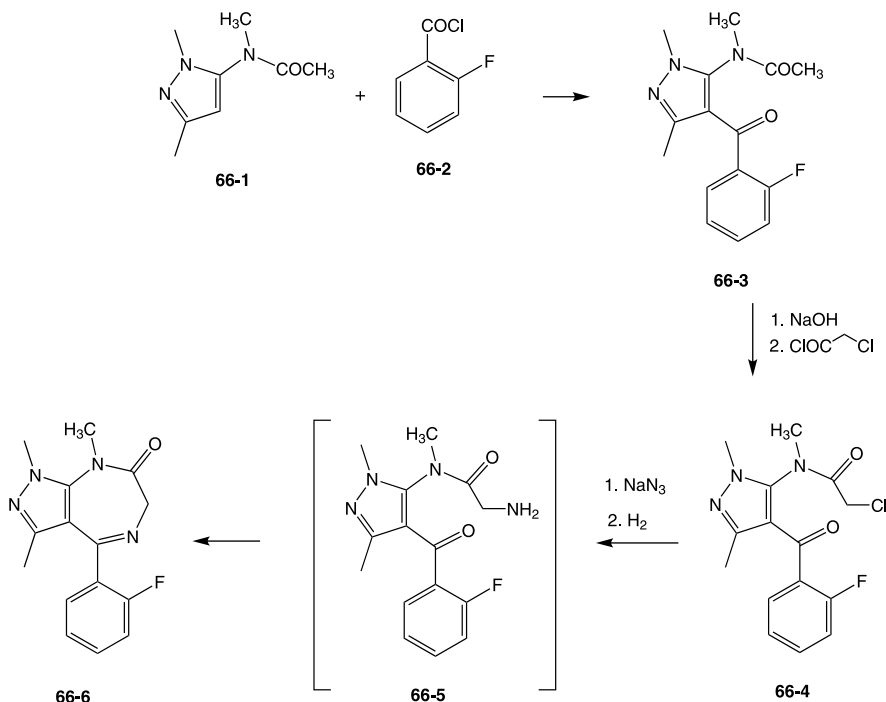
The large increase in potency that is obtained by fusing an additional heterocyclic ring onto the seven-membered ring of benzodiazepines is observed as well in the heterodiazepines. The required diazepinone (**67-2**) is prepared from the thiopheno-phenone (**67-1**) by exactly the same sequence as that used above. Construction of the fused triazole ring follows the method used for **triazolam** (Chapter 12). The

amide in (**67-2**) is thus converted to the corresponding thioamide (**67-3**) (shown in enol form) by treatment with phosphorus pentasulfide. Addition-elimination of hydrazine then leads to the *N*-aminoamidine (**67-4**). Condensation of this last intermediate with ethyl orthoacetate closes the last ring and affords the very potent anxiolytic agent **brotizolam** (**67-5**) [69].
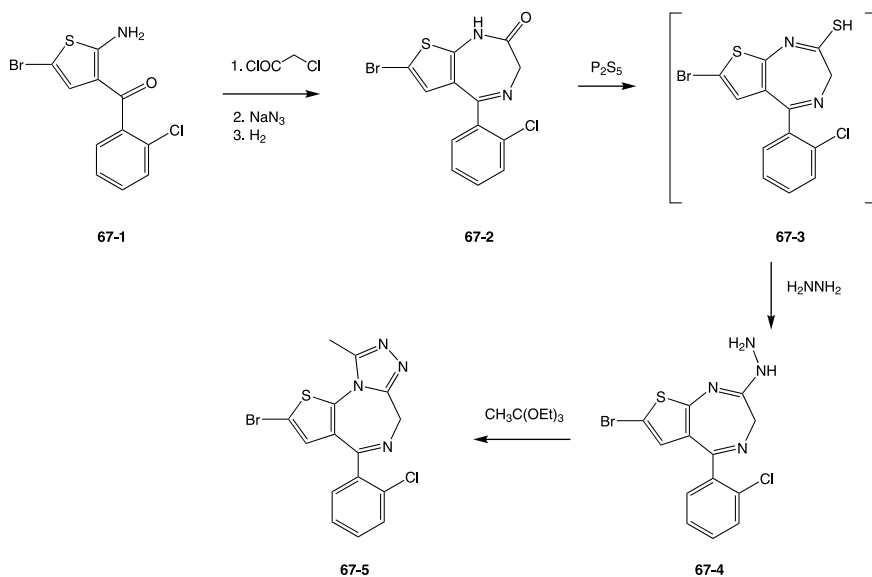
15.5. HETEROCYCLIC COMPOUNDS WITH THREE OR MORE RINGS

A small group of polycyclic compounds defy ready classification on a chemical or, for that matter, pharmacological basis. It must be assumed that they showed enough promise in various experimental test systems to be at least considered for clinical trials. Though few of these seem to have been commercialized as a drug, their preparation nonetheless presents interesting chemistry.

The clinical and commercial success of the antidepressant compound **fluoxetine** (Chapter 2; Prozac) engendered considerable work in other laboratories. A benzo-dioxan based compound that shows similar activity shares only a few structural features with the prototype. The benzodioxan nucleus (**68-3**) is formed by an alkylation reaction between the fluorocatechol (**68-1**) and the derivative (**68-2**) from *meso*, and hence achiral, butanetetrol. The benzyl protecting groups are then removed by hydrogenation over palladium, and the thus-obtained diol is converted to the *bis*-toluene-sulfonate (**68-4**) by reaction with toluenesulfonyl chloride. Treatment of that intermediate with benzylamine leads to *bis*-alkylation on the same nitrogen to form a pyrrolidine ring and thus the tricyclic compound (**68-5**). A second hydrogenolysis step then leads to **fluparoxan** (**68-6**) [70].

Bn = CH₂C₆H₅
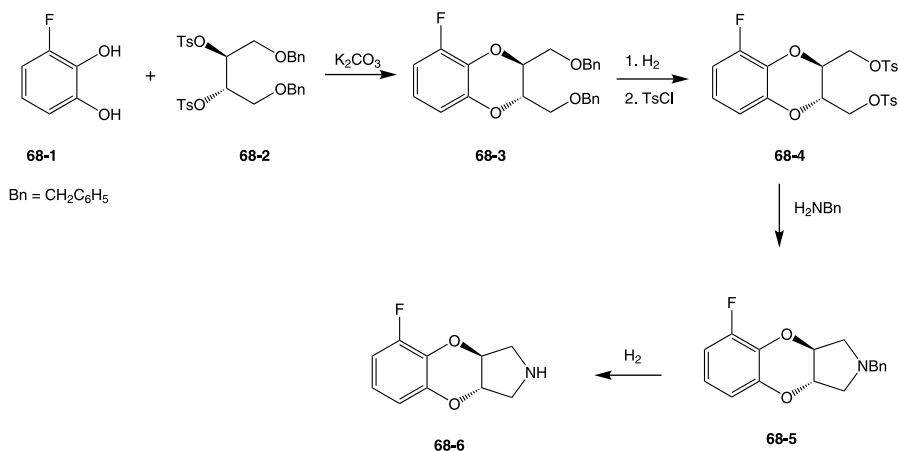
The starting material for the tricyclic NSAID **meseclazone** (**69-5**) consists, appropriately, of chlorosalicylic acid (**69-1**), which has NSAID activity in its own right. Reaction of the acid with hydroxylamine gives the hydroxamic acid (**69-2**). Treatment of that product with the diethyl acetal from 4-chlorobutyraldehyde (**69-3**) gives the derivative (**69-4**), which is in effect a carbinolamine derivative of the aldehyde. Exposure to a mild base results in the formation of the final ring by displacement of the terminal side chain chlorine by the hydroxylamine oxygen [71]. It is not at all unlikely that the product, **meseclazone** (**69-5**), is actually converted back to the salicylate (**69-1**) *in vivo*.
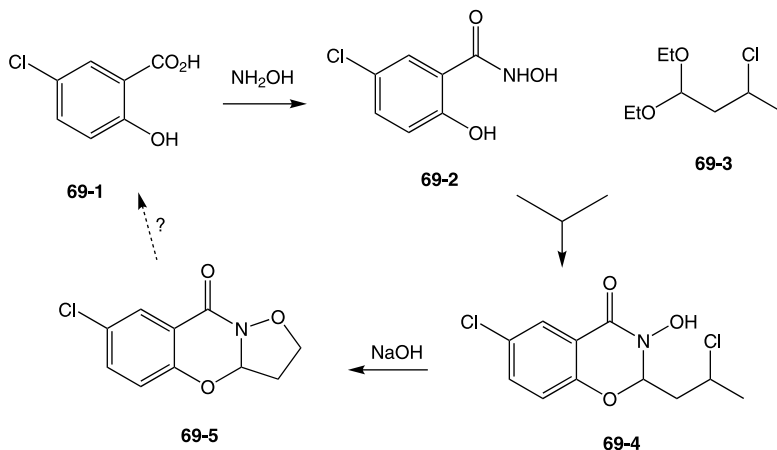
Compounds derived from indole have been extensively investigated as potential psychoactive drugs. The construction of a tricyclic indole derivative starts by benzyltrimethylammonium hydroxide catalyzed Michael addition of 2-carbethoxy-indole (**70-1**) to acrylonitrile to give the adduct (**70-2**). In one of several alternatives

for the next step, the nitrile is then hydrogenated in the presence of acetic anhydride to afford the acetamide (**70-3**). Reaction of that compound with sodium hydride leads to the formation of an anion on amide nitrogen; this attacks the carbethoxy group to form the diazepinone ring. The imide presumably hydrolyses on workup to give (**70-4**) as the observed product. The amide carbonyl group is then reduced with lithium aluminum hydride to give the antidepressant **azepindole** (**70-5**) [72].
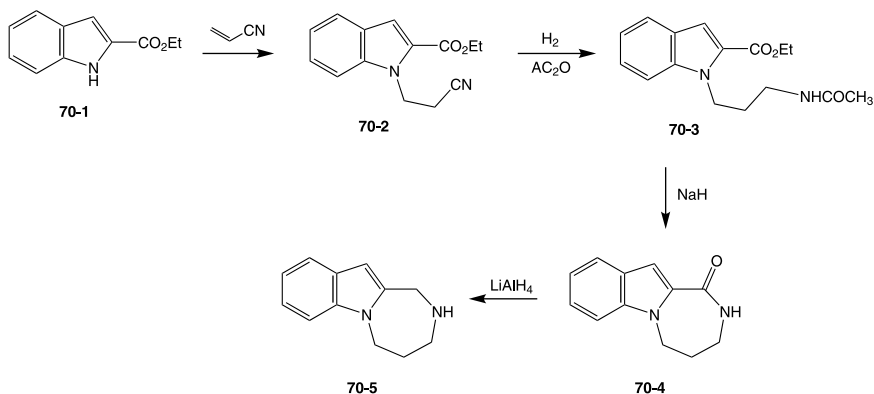
Reaction of methylaminoindole (**71-1**) with ethylene oxide leads to a ring opening of the oxirane with the consequent formation of the hydroxyalkylated product (**71-2**). The reaction interestingly stops at the addition of a single hydroxyethyl unit. This undergoes Friedel–Crafts-like ring closure on treatment with a strong acid to give the tricyclic derivative (**71-3**). Alkylation of the secondary amino group with 3-(3-chloropropyl)pyridine (**71-4**) gives **gevotroline** (**71-5**) [73], a compound that shows antipsychotic activity.
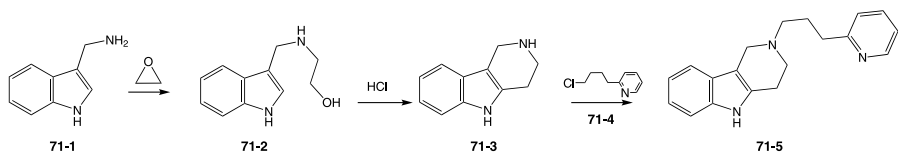
A rather more complex tertracyclic indole based compound lowers blood pressure by selective blockade of α_1-adrenergic receptors. Reaction of the anion from indole (**72-1**) with butyrolactone (**72-2**) leads to the scission of the carbon–oxygen bond in the reagent and the formation of the alkylated product (**72-3**). The acid is then cyclized onto the adjacent 2 position to give the ketone (**72-4**) by treatment with a Lewis acid such as polyphosphoric acid. Reaction with bromine then leads to the brominated ketone (**72-5**). This is subjected to reductive alkylation with ethylene

diamine and sodium borohydride. The reaction may involve either initial imine formation or displacement of halogen. Intermediate (**72-6**), which would form if the latter prevails, will then undergo reductive alkylation at the carbonyl group. Thermodynamic control of the final reduction step would account for the formation of the observed *trans* fused product (**72-7**). The very different steric milieu of the two nitrogens is illustrated by the fact that reaction of the piperazine (**72-8**) with isopropyl bromide proceeds selectively at the more open amine to give the mono-alkylated product (**72-8**). The remaining secondary amine is then converted to the more reactive anion; treatment of that with ethyl bromide affords **atiprosin** (**72-9**) [74].
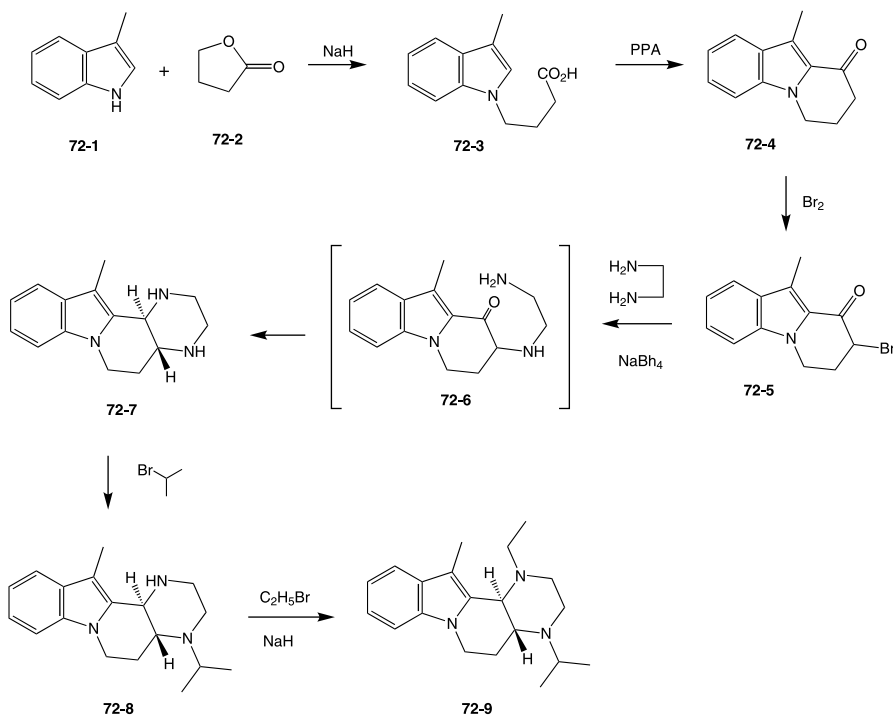
The very versatile synthon isatin (**73-1**) provides the starting material for a fused heterocyclic compound that has been investigated as an antiallergic agent on the strength of its activity as a mediator release inhibitor. Oxidation of the hydrazone (**73-2**) from isatin with mercuric oxide gives the diazo derivative (**73-3**). Treatment of this reactive intermediate with the dipolarophile propynal leads to 1,3-dipolar cycloaddition and thus the formation of the *spiro*-pyrrazole (**73-4**). This intermediate undergoes spontaneous rearrangement to a planar conjugated isomer. Migration of the indolone bond leads to ring enlargement to the quinolone (**73-5**). Reduction of the aldehyde with sodium borohydride gives the corresponding carbinol and thus **pirquinozol** (**73-6**) [75].
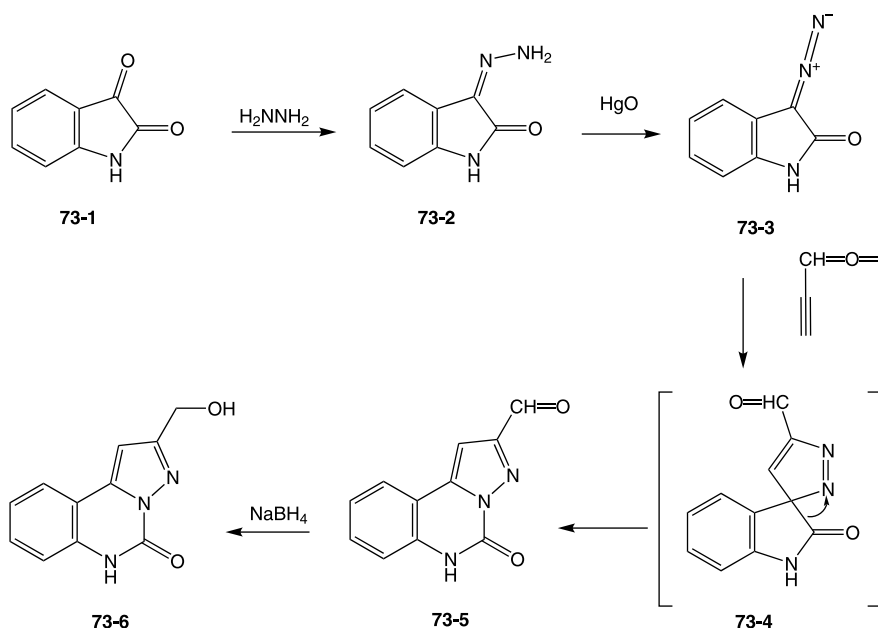
Though the synthesis of the tricyclic CNS agent **piquindone** (**74-6**) does not involve an indole, a partly reduced form of this moiety is imbedded in the final structure. The route to this compound starts with the alkylation of the acetal (**74-1**) from 3-acetylpyridine with methyl iodide to give the corresponding quaternary salt. This is reduced to the tetrahydropyridine on treatment with sodium borohydride. Hydrolysis of the acetal protecting group then affords the conjugated ketone (**74-2**). Reaction of that product with the anion from ethyl malonate initially gives the transient Michael adduct (**74-3**). The reversible nature of this reaction assures the formation of the thermodynamically favored *trans* (diequatorial) product.
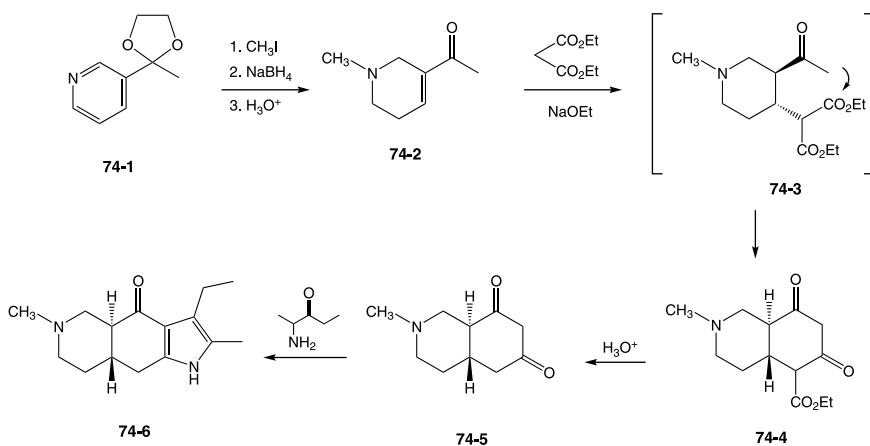
The anion formed from the acetyl methyl group under reaction conditions then attacks one of the carbethoxy groups to form a cylohexanone to give (**74-4**) as the isolated product. The free acid obtained on hydrolysis of the ester decarboxylates to give the β-diketone (**74-5**). In a classic application of the Knorr pyrrole synthesis, the diketone is then allowed to react with 2-aminopentan-3-one. Since the latter is unstable, it is generated *in situ* by reduction of the nitrosation product from diethyl ketone. There is thus obtained **piquindone** (**74-6**) [76], a compound that displays antipsychotic activity.

The pyrimidinoquinoline ring system provides the nucleus for yet another anti-allergic mediator release inhibitor. Knoevnagel condensation of the nitrobenzalde-hyde (**75-1**) with cyanoacetamide gives the cinnamide (**75-2**) (no stereochemistry implied by the depiction). The nitro group is then reduced by treatment with iron in acetic acid. Exposure of the product (**75-3**) to a base leads to the addition of the aniline nitrogen to the nitrile with the consequent formation of the quinoline (**75-4**). The last ring is then formed by reaction of the aminoamide with diethyl oxalate. This affords the pyrimidone ring and thus **pirolate** (**75-5**) [77].
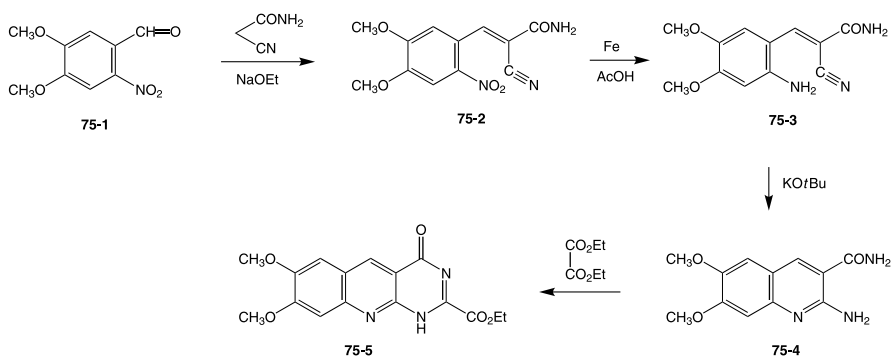
The stereoselective nature of drug action should not be unexpected in view of the fact that all structures with which those compounds interact, receptors and enzymes,
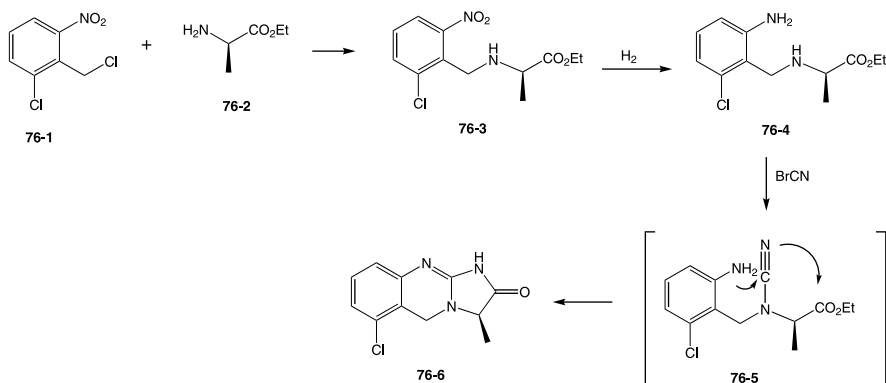
are composed of chiral amino acids. The synthesis of the platelet aggregation inhibitor **quazinone** (**76-6**) thus incorporates the chiral moiety leading to the active isomer in an early step. Thus, displacement of halogen in the benzyl chloride (**76-1**) with ethyl D-alaninate (**76-2**) affords the alkylated derivative (**76-3**) in chiral form. The nitro group is then reduced to the corresponding aniline (**76-4**). Reaction of this product with cyanogen bromide leads to a reaction at the more basic, aliphatic amine to give the transient cyanamide (**76-5**). On heating that intermediate reacts further; the aniline nitrogen adds to the newly introduced cyano group; the thus-formed imine then displaces ethoxide from the adjacent ester to form the imidazolone ring. The end product of this cascade is the imidazo quinazoline **quazinone** (**76-6**) [78].

The involvement of the immune system in a host of diseases has led to a search for compounds that modulate that system and thus hopefully change the course of the disease. An angular imdidazoquinoline has shown some activity as an immune modulator. The synthesis of this compound starts with the nucleophilic aromatic displacement of chlorine in the quinoline (**77-1**) by *iso*butylamine. Reduction of the nitro group then affords the 3,4-diamine (**77-3**). The imidazole ring is formed in the usual way by reaction with ethyl orthoformate to afford the tricyclic intermediate (**77-4**). Introduction of the requisite amino group at position 2 starts by the oxidation of quinoline nitrogen with hydrogen peroxide to the *N*-oxide (**77-5**). Treatment with phosphorus oxychloride leads to the 2-chloro derivative (**77-6**) by the familiar variant on the Polonovski reaction. Ammonolysis of this last intermediate in aqueous ammonia affords **imiquimod** (**77-7**) [79].

77-1 iBuNH$_2$ **77-2**, R = O   **77-3**, R = H   H$_2$ CH(OEt)$_3$ **77-4**

H$_2$O$_2$

77-7   NH$_4$OH   **77-6**   POCl$_3$ **77-5**
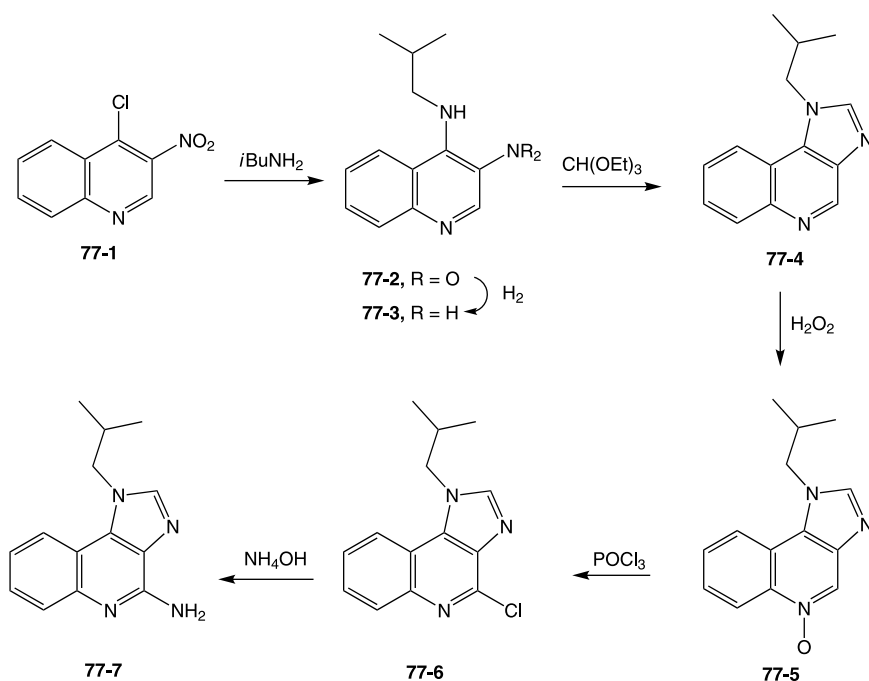
Modified purines, as noted earlier in this chapter, comprise the majority of the PD-5 inhibitor compounds aimed at erectile dysfunction. The structure of yet another drug for this indication, **tadalafil (78-6)**, differs markedly from the proto-types. Tryptophan methyl ester (**78-1**) provides the starting material for large-scale enantioselective synthesis. Condensation of that compound with piperonal (**78-2**) in the presence of an acid leads to the formation of the tricyclic intermediate (**78-3**). This transform involves an initial addition of the amine to the aldehyde. The carbocation from the newly formed carbinolamine then attacks the indole 2 position to form the the fused piperidine. The stereochemistry of the new chiral center is guided by that from the tryptophan carbon across the ring. The secondary amine is next acylated with chloroacetyl chloride in the presence of triethylamine to afford (**78-4**). Reaction of this intermediate with methylamine goes on to form the desired product in a single step. This reaction can be rationalized by assuming the initial displacement of terminal chlorine by the amine to give the transient inter-mediate (**78-5**). This amino group then takes part in an ester-amide interchange In the presence of a base to form the new ring. There is thus obtained **tadalafil (78-6)** [80].
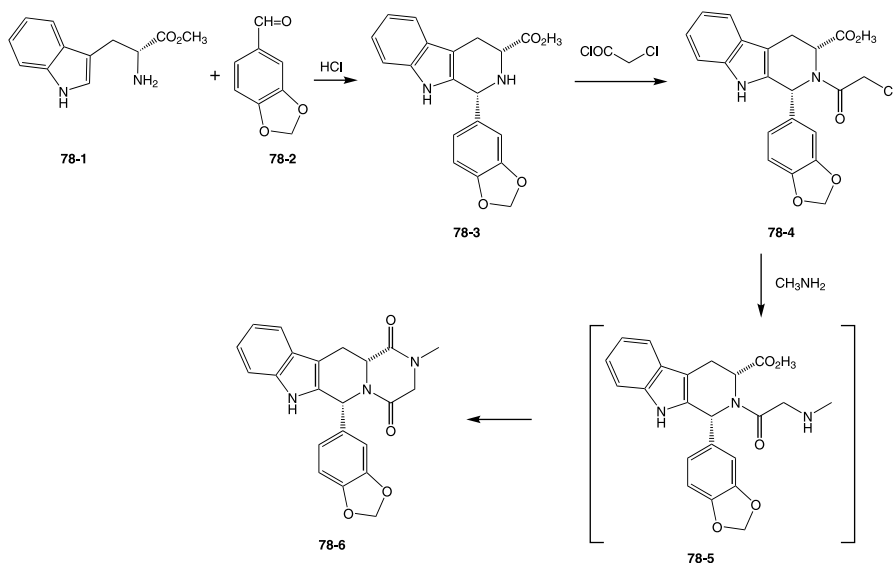
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SUBJECT INDEX

Bold numbers denote syntheses.

REACTION INDEX

CROSS INDEX OF BIOLOGICAL ACTIVITIES